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THE PATERSON-BROWN KELLY SYNDROME

ITS RELATIONSHIP TO IRON DEFICIENCY AND POSTCRICOID CARCINOMA

PART I

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THIS syndrome, in which dysphagia is associated with hypochromic anæmia, has been well known under a variety of names, for the past forty years. A considerable volume of literature on the subject has been published during that time and this is reviewed under various headings.

General Survey of the Literature

Although other writers had previously described some features of the condition, Paterson and Brown Kelly at a meeting of the Royal Society of Medicine in 1919 gave the first comprehensive description of the syndrome. Their names have been attached to the syndrome in this country, but in the United States of America it is usually referred to as the Plummer-Vinson syndrome, while in Scandinavia the term *sideropenic* dysphagia is used. Plummer partially described the syndrome in 1914 and Vinson amplified this description in 1922—they both believed the dysphagia was an hysterical manifestation. The term sideropenic dysphagia was suggested by Waldenstrom (1938), who believed the basic cause was iron deficiency.

Studies on series of these patients confirmed the original findings, viz: 1926, Moersch and Conner; 1927, Brown Kelly; 1928, Jones and Owen; 1929, Cameron; 1931, Paterson; 1932, Graham and Johnson.

In 1936 Ahlbom published an investigation of 150 cases of carcinoma

of the upper alimentary tract in women and showed a high proportion of them had a preceding Paterson-Brown Kelly syndrome.

Other writers (Simpson, R. (1939), Videback (1944), author (1957)) have pointed out that multiple primary carcinomata may develop anywhere in the upper alimentary tract in these patients.

Owen (1950) gave a comprehensive review of the relationship between the Paterson-Brown Kelly syndrome and postcricoid carcinoma.

Until 1940 the great majority of papers on the subject had come from the United States, Scandinavia and Great Britain. It was believed at that time that the condition had a racial incidence, being found mainly in those of Anglo-Saxon descent, and that it was more or less unknown in Latin, Slav and Asiatic countries. Since then, however, a considerable number of papers on the condition and descriptions of cases have appeared in journals in France, Italy, Belgium, Poland, Spain, Holland, Czechoslovakia and South America. (See references Appendix 1.) The general opinion as expressed in these papers is that the condition is by no means as rare in these countries as had previously been thought and that many cases had probably been missed in the past.

Description of the Syndrome

A well developed case presents a typical picture.

The patient is usually a small, "shrunken" middle-aged female.

She gives a history of difficulty in swallowing, mainly for solids, and this "small swallow" has often been present for as long as she can remember. As a result, the diet is semi-solid with a high carbohydrate and low protein content. Many patients have had an incident in the past when a solid particle, such as a piece of meat or nut has got stuck in the upper gullet, and the resultant choking fit has made them nervous, slow eaters.

In addition to the dysphagia, many of these patients will give a history of anæmia and complaints of soreness of the tongue and mouth, flatulence and dyspepsia are common. A few also suffer from diarrhœa and paræsthesiae.

On clinical examination koilonychia, cheilosis and edentia are usually obvious, while dryness of the skin and dry, brittle hair are noted in many cases. The tongue is smooth and red and the mucosa of the pharynx as seen with the laryngeal mirror may appear pale and atrophic. Splenomegaly and sometimes hepatomegaly may be present.

The blood picture is that of hypochromic microcytic anæmia, though in a few recorded cases hyperchromic anæmia has been found.

Gastric analysis shows complete achlorhydria in many cases.

Barium swallow examination may reveal a web formation in the hypopharynx or an area of constriction several centimetres in length in the same region.

Direct pharyngoscopy may show atrophic mucosa in the hypopharynx, fissures and slight superficial ulceration. A web, if present, is seen as a thin, crescentic membrane, usually arising from the anterior or lateral walls of the hypopharynx and stretched across the lumen which is narrowed to a variable extent. Alternatively, there may be a marked narrowing of the gullet for several centimetres at the same level.

In one recorded case with persistent diarrhœa sigmoidoscopy revealed atrophic changes in the mucosa of the colon (Graham and Johnson, 1932).

In another single recorded case with very severe iron deficiency anæmia there were vaginal changes similar to those seen in the mouth and pharynx (Ezes, H. 1951).

Incidence of Stigmata in Paterson-Brown Kelly Syndrome

Few cases of this syndrome will exhibit all the symptoms and signs described above. In order to diagnose the condition, only dysphagia with some of the accompanying signs and symptoms is necessary. An analysis of the incidence of the accompanying stigmata in four different series of cases is given below.

TABLE I.

	No. of Cases	Dysphagia	Glossitis	Cheilosis	Anæmia	Achlorhydria	Koilonychia	Splenomagaly	Abnormal Ba. Swall.
		%	%	%	%	%	%	%	%
Moersch & Conner (U.S.A.) 1926	65	100	15	Common	100	80 in 10 cases	—	30	—
Sotgiu & Labo (Swiss) 1956	37	100	5	70	41	84	40	—	40
Wynder *et al.* (Sweden) 1958	150	100	38	62	77	—	38	—	—
Author (1959)	94	100	70	38	100	90	50	23	50 of 39 cases

Averaging up the findings in these four series it will be seen that the stigmata occur in the following order of frequency: Anæmia and Achlorhydria in approximately 80-90 per cent., Cheilosis 60-70 per cent. Glossitis 50-60 per cent., Koilonychia 40-50 per cent., Splenomegaly 20-30 per cent. In addition about half the cases will show abnormalities on barium swallow examination.

Incidence of Stigmata in Hypochromic Anæmia

If one considers all cases of hypochromic anæmia, then the various stigmata occur with the following frequency according to two recorded series. As will be seen, dysphagia occurs in 10-13 per cent. of all cases of hypochromic anæmia.

TABLE II.

	No. of Cases	Dysphagia	Achlorhydria	Glossitis	Splenomegaly	Koilonychia
		%	%	%	%	%
Davidson, 1938	125 (severe)	10	66	30	27	17
Witts, 1931	117	13	81	50	30	—

Screening 2,012 cases of hypochromic anæmia seen in the Hæmatology Department of Manchester Royal Infirmary produced 106 cases with dysphagia, an incidence of 5 per cent.

Associated Syndromes

Sjogren's syndrome is found in post-menopausal women. It consists of polyarthritis and failure of lacrimal and salivary secretion due to disintegration of the parenchyma of the affected glands. The lack of secretion leads to "dry eyes" and dryness of the mouth and throat.

Godtfredsen (1947) investigated 23 cases of this syndrome and found evidence of Paterson-Brown Kelly syndrome in 13 cases. The majority of these had iron deficiency anæmia and achlorhydria and 3 showed a web formation on barium swallow examination.

Flusser *et al.* (1954) believes Sjogren's syndrome and Paterson-Brown Kelly syndrome are two manifestations of a similar deficiency disease and describes them as the sialopenic and sideropenic forms respectively.

Hunner's ulcer of the bladder may possibly be related to the Paterson-Brown Kelly syndrome. Robb (1941) reports two cases of the former conditions, both showing marked iron deficiency anæmia and one having a well-developed Paterson-Brown Kelly syndrome and a history of a previous pre-cancerous lesion in the mouth.

Ætiology of the Syndrome

Many different theories have been advanced for the causation of the syndrome.

In particular three causative factors have received considerable support from writers on the subject namely (1) primary dysphagia, (2) riboflavin deficiency, and (3) iron deficiency.

(1) *Primary Dysphagia.*

Those who support this theory believe that the dysphagia, due to a "stricture" in the hypopharynx, causes the patient to modify her diet, producing iron and vitamin deficiencies which result in the development of hypochromic anæmia and the other stigmata of the condition.

Most of the early writers on the subject believed in this sequence of events. Bronner (1913) ascribed the development of the hypopharyngeal stricture to the repeated trauma of swallowing a hard bolus, while others (Jones and Owen (1928), Kelly (1919), Moersch (1926), McKenzie (1918) and Paterson (1919) believed it was due to spasm, and Plummer (1914) and Vinson (1922) thought it was an hysterical manifestation. Hurst (1926) believed streptococcal infection caused the narrowing of the hypopharynx.

By 1937, however, Paterson had doubts that the dysphagia was the primary change and he then emphasized the importance of iron therapy.

(2) *Riboflavin Deficiency*

The buccal and tongue changes and the angular stomatitis seen in this syndrome suggested a riboflavin deficiency. Simpson, J. (1939), Videback (1944), Pollack (1945) and Savilahti (1946) all believe that riboflavin deficiency plays an important rôle in the development of the syndrome. Ferrando-Botet (1949) suggests that it is a lack of Vit. B_2 complex which is particularly important.

Murphy (1940), Jankelson (1940) and Meulengracht (1941) report cases of the syndrome successfully treated with riboflavin.

Franschetti (1943) treated cases of Sjogren's syndrome with Vit. B complex with favourable results.

Against this theory is the fact that cases of true riboflavin deficiency as described by Jehgers (1942) differ from the Paterson-Brown Kelly syndrome in that ocular manifestations are common, while dysphagia is rare. The tongue is a magenta-colour, unlike the smooth, red tongue seen in Paterson-Brown Kelly syndrome.

(3) *Iron Deficiency*

The majority of writers on the subject in recent years have considered a primary iron deficiency as the basic cause. They believe this can lead to changes in the mucosa of the upper alimentary tract and to dysphagia. The iron deficiency also causes hypochromic anæmia, angular stomatitis and koilonychia, and may be responsible for atrophic changes in the gastric mucosa. They accept the fact that there may also be some degree of riboflavin deficiency, probably as the result of the modified diet.

Leblond and Stevens (1948) have shown that the surface cells in the intestinal epithelium of rats are renewed every one and a half days.

Iron and riboflavin are important for the formation of cellular enzyme systems, and it is thought that a lack of these substances can interfere with cellular regeneration in the epithelium of the upper alimentary tract. Cojazzi (1949) claims to have confirmed this experimentally. Cordray (1940) fed rats on an iron-free diet and produced histological changes in the mucosa of the gullet, but noted no submucosal fibrosis.

Many writers (Cahn (1952), Cameron (1929), Henderson (1954), Hoover (1935), McGibbon (1935) and Witts (1956)) believe that iron deficiency is the basic cause, although Ahlbom (1936) thinks the condition may differ in some respects from the normal hypochromic anæmia, and Graham and Johnson (1932) noted an increased fragility of red cells in five out of their six cases.

It was Waldenstrom in 1938 who first suggested that the changes in the mucosa and nails could occur without anæmia, but with a low serum iron, and that iron therapy alone would cure many cases and reverse the epithelial and nail changes. For this reason he suggested the condition be named sideropenic dysphagia.

In 1944 Glazebrook described a case of polycythæmia rubra vera who had a low serum iron and koilonychia. He believed the sideropenia was due to the excessive demands for iron for hæmoglobin formation. After treatment by irradiation of the bone marrow the serum iron rose from 50 micrograms per 100 ml. to 320 micrograms per 100 ml., and the koilonychia recovered.

Darby (1946), in a convincing article on the causation of the oral lesions in hypochromic anæmia, details six such cases, two of which also had dysphagia. Four of these failed to respond to Vit. B therapy, while all responded satisfactorily to iron therapy alone. He was careful to see that the patients' diets remained unaltered during treatment. He points out that one may get oral lesions in hypochromic anæmia without dysphagia and with an adequate diet. Also, that in most nutritional surveys the oral lesions have been found to be associated more commonly with low hæmoglobin levels than with Vit. B. deficiency.

Sacrez *et al.* (1954) records an interesting case of a child four years of age who had œsophageal strictures, one in the middle and one in the lower third of the gullet, probably congenital in origin. As a result, the diet was entirely fluid from birth and when first seen the child was pale and wasted with marked glossitis and a hæmoglobin level of 30 per cent. Dilatation of the strictures allowed a normal diet to be taken, but no improvement was noted in the blood picture or the glossitis and the child continued to complain of some dysphagia. Iron therapy was started and within two months the hæmoglobin level was 70 per cent. and the glossitis and dysphagia had completely resolved, although barium swallow examination showed very little change in the strictures.

Sotgiu and Labo (1956) studied 37 cases of the syndrome. They found

that 84 per cent. had achlorhydria and sideropenia, while riboflavin deficiency, as shown by the riboflavin content of the urine, did not occur unless the dysphagia had been present for longer than one year, and that it was not always present even in cases with longstanding dysphagia. In 45 per cent. of their cases there was a low serum protein and evidence of hæmolysis, and it was suggested that this might be an hitherto unsuspected factor in the condition.

Discussion of Ætiology

Primary dysphagia seems an unlikely explanation of the condition because:

(1) No one has yet produced cases showing the hypopharyngeal changes of web or stricture formation before the development of blood and epithelial changes.

(2) The blood and epithelial changes do not occur in other types of dysphagia, e.g. a benign fibrous stricture caused by swallowing corrosives. (Sacrez's case might be an exception to this observation.)

Two such cases have been investigated and treated in the E.N.T. Department of the Manchester Royal Infirmary during the past two years. Both were females and had suffered from dysphagia for 20 years.

Mrs. E. K., aged 65 years, had two considerable fibrous strictures of the pharynx and a history of swallowing caustics when young. (See X-ray plate.) There was no evidence of anæmia, iron deficiency or any of the stigmata of the Paterson-Brown Kelly syndrome.

Mrs. M. N., aged 56 years, had severe syphilitic cicatrization of the laryngopharynx which narrowed the lumen to approximately the size of a lead pencil and her diet had been semi-solid for many years. In spite of this she was well covered and had no anæmia nor evidence of iron deficiency. There were none of the stigmata of the Paterson-Brown Kelly syndrome.

(3) The blood and epithelial changes in the mouth and nails frequently occur in iron deficient states without dysphagia.

(4) The sex incidence is similar to that of iron deficiency anæmia.

(5) Dilatation by itself improves many cases, but not so effectively as when combined with iron therapy.

Riboflavin deficiency, whilst present in some cases, is absent in others and is, therefore, unlikely to be the basic cause of the condition. The clinical features of the syndrome differ in several respects from those of a pure riboflavin deficiency, particularly in the absence of kerato-conjunctivitis, and in the colour of the tongue.

Meulengracht, Murphy and Jankelson have reported cases successfully treated with riboflavin, but there seems some doubt in all these papers as to whether or not iron was also administered. Jankelson's cases resembled pure riboflavin deficiency, rather than a true Paterson-Brown Kelly syndrome.

Iron deficiency is considered the most important causative factor because:

(1) Most investigators have found a marked iron deficiency in these patients, either with or without an associated hypochromic anæmia.

(2) Iron deficiency can cause the changes in the nails and buccal mucosa without any dysphagia.

FIG. 1. Part 1.

(3) Iron therapy alone resolves the symptoms in many cases and has been shown to reverse the epithelial changes in the mouth, nails and probably the stomach also.

(4) The sex incidence of the Paterson-Brown Kelly syndrome is the same as that of iron deficiency anæmia.

(5) Experimental work with rats showed that iron deficiency can produce histological changes in the mucosa of the gullet similar to those seen in the Paterson-Brown Kelly syndrome, though no submucosal fibrosis developed.

Apart from these three major theories for the causation of the syndrome, various other factors have been emphasized by certain writers on the subject.

Ahlbom (1936) and Wynder *et al.* (1957) have noted a high incidence of early edentia. Twenty-three per cent. of cases studied by Wynder *et al.*, had lost all their teeth before the age of thirty years.

Graham and Johnson (1932) and Sotgiu and Labo (1956) have noted changes in the blood suggesting a possible abnormality in the red cell fragility.

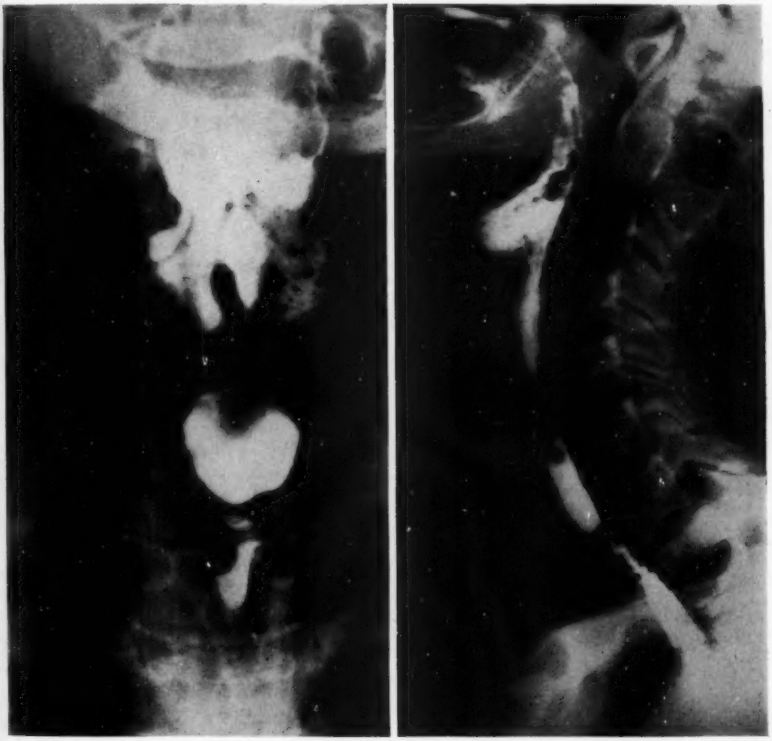


FIG. 2. Part 1.

Flusser *et al.* (1954) believe that sideropenia, ariboflavinosis, pellagra, sprue, the Paterson-Brown Kelly syndrome and Sjogren's syndrome are all related, there being a primary defect in the formation of co-ferments for tissue respiration ferments. The saliva may play an important rôle in the formation of apoferments of some of the B groups of vitamins. Cameron (1929) found the pH of the saliva within normal limits in his 25 cases.

Histological Changes in the Hypopharynx

The histological changes have been reported by Suzman (1933), Savilahti (1946), Owen (1950) and Guichard *et al.* (1950) from post mortem material. McGee and Goodwin (1938) report post mortem findings in an atypical case. Except for this latter case, the writers found similar changes in the hypopharynx. These consisted of atrophy and thinning of the

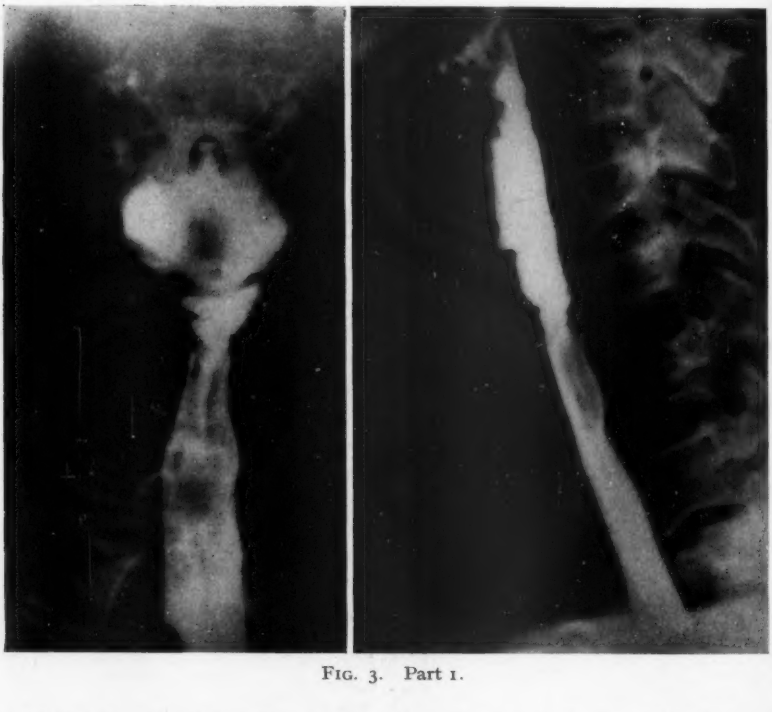


FIG. 3. Part 1.

epithelial layers with other areas of hyperkeratinization, while the submucosa was infiltrated with chronic inflammatory cells, especially where the overlying mucosa was much thinned. The appearance of the muscular layer varies from degenerative and atrophic changes to fibrosis.

Hoover (1935) shows a microphotograph of a biopsy through a web and this consists of a fibrous tissue core with a layer of mucosa on each side.

Reversibility of the Histological Changes

Successful iron therapy may reverse the nail changes as noted by Waldenstrom (1938). This also occurred in the case reported by Glazebrook (1944).

Darby (1946) found that the macroscopic changes in the tongue recovered to normal with iron therapy, and Witts (1956) states that the lesions in the upper alimentary tract recover with satisfactory treatment, and recover completely in the case of the tongue. He also says that there may be permanent damage to the mechanism of swallowing.

Guichard *et al.* (1952) recorded the post mortem findings in a female patient of 83 years who, nine months before her death, had intensive oral and intravenous iron therapy for 3 months with relief of dysphagia, although her blood count and barium swallow appearances never changed. They found the following changes in the hypopharynx: (1) considerable desquamation of the epithelium; (2) atrophy of the mucosa and deep prolongation of the epithelial papillae; (3) atrophy of the submucosa with areas of chronic inflammation and vasodilatation and (4) œdema and some atrophic changes in the muscle layers. In this case, therefore, the intensive iron therapy, although relieving the dysphagia, had not reversed the histological changes.

Several authors report the result of investigations into the reversibility or otherwise of the changes in the gastric mucosa (Badenoch *et al.* (1957), Davidson, L. S. *et al.* (1938), Hallen (1938) and Leonard (1954). All found evidence of return of function in some of their cases after prolonged iron therapy. It was usually the young adults who responded satisfactorily. On the other hand, Lees and Rosenthal (1938) could find no return of gastric function in 21 cases after a year's iron therapy.

There is, therefore, some evidence that suitable treatment can reverse the histological changes in the gastric mucosa in young people, but it seems less likely that this can occur in older patients where the changes are more marked and well established. This was true of hypopharyngeal changes in the case reported by Guichard *et al.* (1952). The nail and buccal changes seem to be reversible with treatment in most cases.

The X-ray Changes in the Hypopharynx and Œsophagus in Paterson-Brown Kelly Syndrome

The typical X-ray changes and the best way for demonstrating these were described by Waldenstrom and Kjelborg (1939). A web, or rarely, multiple webs may be seen on barium swallow examination. The usual position is anteriorly in the post-cricoid region, but occasionally they occur lower down the cervical œsophagus (Videback (1944), Thornval (1948)). In very advanced cases, there may be a broader, cuff-like stricture below the web, caused by fibrous infiltration of the œsophageal wall. Such a condition is well illustrated by the following case.

Mrs. H. S., aged 46 years, attended the out-patients' department in March 1960 complaining of increasing dysphagia for 20 years so that her diet was now restricted to fluids only. She had taken iron intermittently over a long period

of time. Her menses had always been very heavy. Her hæmoglobin when first seen was 60 per cent. and the serum iron 55 micrograms per 100 cc. She had marked glossitis, cheilosis and kiolonychia and her barium swallow showed the following result.

Treatment by intravenous iron improved her blood picture so that the hæmoglobin rose to 84 per cent. in 5 weeks. There was, however, no change in her swallowing. A radium menopause was performed in April 1960 and forcible dilatation of the stricture was carried out in May 1960. After the dilatation her swallowing and general condition rapidly improved. She put on two stone in weight in 4 months. When seen in September 1960 she was swallowing well, the tongue had nearly returned, to normal hæmoglobin 92 per cent. and serum iron 165 micrograms per 100 cc. The barium swallow showed a good lumen in the area of the previous stricture, but a small web was present, now more easily seen than in the previous film and situated just above the area of the stricture.

Holmgren (1943) and Lindvall (1953) agree that malignant change usually occurs just above the site of the web and suggest this may be due to irritation of food stasis at this point.

The Treatment of Paterson-Brown Kelly Syndrome

The treatment will depend on one's concept of the ætiology. As previously shown, the cause of the syndrome has been attributed to primary spasm or stricture of the hypopharynx, riboflavin deficiency and iron deficiency, and the respective treatments are, therefore, dilatation, riboflavin or iron therapy.

Vinson (1940) believes that hysterical spasm is the primary cause and treats his cases by reassurance and bouginage, the latter being performed for its psychological rather than its physical effects. He says iron is not essential, but can be given to correct the secondary anæmia, but the blood picture took a long time to return to normal in his cases and one-third of them relapsed. Some needed many dilatations.

Many workers (Bingham, *et al.* (1953), Bronner (1913), Flett *et al.* (1946), Jones, A. M., *et al.* (1948), Kelly (1919), Moersch, *et al.* (1926) and McKenzie (1918) have emphasized the importance of dilatation, considering this to be the most important single step in the treatment of the condition. This can be done slowly with graduated bougies, but is often achieved by rupturing the web by passage of the œsophagoscope.

Ellenberg and Pollack (1942) state that true ariboflavinosis should be cured by three weeks' treatment with 0·25-0·75 mgms. of riboflavin per kilogramme body weight. Murphy (1940), Jankelson (1940) and Meulengracht (1941) have all claimed successes with riboflavin therapy.

Paterson (1937), Waldenstrom (1939), Nowak (1951), Cahn (1952), Sotgiu (1956), and Witts (1956) believe that iron therapy is the essential part of the treatment. The dysphagia will respond to this treatment alone in many cases, though others may also require dilatation.

Iron therapy, if it is to be effective, must be prolonged and, if necessary, maintained indefinitely (Cahn, 1952), and large doses of up to 15 grs. ferrous sulphate thrice daily are indicated in the first instance (Jasinski (1949), Mettier *et al.* (1929), Paterson (1937) and Witts (1931). These cases are liable to relapse if therapy is stopped, and the cause will often be continued blood loss, e.g. menorrhagia, so that it is essential to do everything possible to correct this or the iron therapy will be ineffective. The addition of ascorbic acid to the iron will aid its absorption. The iron stores may not be replenished even when the blood picture has returned to normal, so that therapy should be continued for some time beyond this point and perhaps reinforced by intravenous iron therapy (Davidson, W. M., 1952).

Many writers suggest that a combination of all three methods of treatment will be required in some cases, i.e. iron and riboflavin therapy and dilatation. The latter is necessary if submucosal fibrosis has occurred in the gullet to a degree that seriously hampers the swallowing of a normal bolus. A few cases will be resistent to all treatment, requiring repeated dilatation (Owen, 1950).

Several other methods of treatment have been suggested by various authors—(Ferrando Botet (1949), Howell *et al.* (1953), Sotgiu and Labo (1956), Szenes (1949), and Tafana (1959)).

Iddles (1954) records a case in whom the stenosis of the hypopharynx was so severe that dilatation via an endoscope was impossible. External exploration and myotomy of the cricopharyngeus down to the mucosa brought complete relief of symptoms.

The Relationship of the Paterson-Brown Kelly Syndrome to Postcricoid Carcinoma

The belief that such a relationship exists is based on the following points:

(1) Many cases of postcricoid carcinoma give a history of preceding Paterson-Brown Kelly syndrome.

(2) A follow-up of cases of the syndrome shows that a significant number develop malignant disease of the hypopharynx.

(3) The sex incidence of postcricoid carcinoma is similar to that of the syndrome and there is thus a reversal of the usual sex incidence for carcinoma of the upper alimentary tract as a whole, which is dominantly male, in the postcricoid region, where 50-80 per cent. of the cases in Sweden and the United Kingdom occur in females.

(4) The histological changes in the hypopharynx seen in some cases of Paterson-Brown Kelly syndrome have pre-cancerous characteristics.

(5) The biochemical changes in cell metabolism probably present in the Paterson-Brown Kelly syndrome have similarities to the biochemical changes in malignant disease.

Early writers on the subject of the Paterson-Brown Kelly syndrome (Bronner (1913), Brown Kelly, (1919) and Paterson (1919)) mentioned the development of malignant disease of the hypopharynx in their patients, though Vinson (1922 and 1940) says it occurs only rarely and does not think the incidence significant.

Cameron in 1929 pointed out the similarity in the sex incidence of Paterson-Brown Kelly syndrome and postcricoid carcinoma.

It was Ahlbom in 1936 who emphasized the importance of preceding Paterson-Brown Kelly syndrome in the development of carcinoma of the upper alimentary tract in females in Sweden. He studied 150 such cases and found 70 per cent. gave a history of preceding Paterson-Brown Kelly syndrome, although he considered even mild preceding dysphagia as sufficient evidence for diagnosis of the syndrome.

More recently Wynder, Hultberg *et al.* (1957) also from the Radium-hummet, Stockholm, studied 472 cases of carcinoma of the upper alimentary tract in males and females. They considered many possible pre-disposing factors including syphilis, tuberculosis, nephritis, diabetes, surgery, diet and the Paterson-Brown Kelly syndrome. The latter was the only significant factor, there being a high incidence in all female cases of carcinoma of the upper alimentary tract in all sites, and also in male cases of carcinoma of the lower hypopharynx.

A similar retrospective study was carried out by Videbaek in Denmark (1944) on 235 cases of carcinoma of the upper alimentary tract in females. He found clear evidence of preceding Paterson-Brown Kelly syndrome in only 6 cases: the sex incidence of carcinoma of the pharynx in Denmark is female: male: 24: 76:—and in Sweden, female: male: 57: 63.

The relative sex incidence for different sites of carcinoma of the upper alimentary tract in various countries has been studied by Ahlbom (1936), Koszarowski (1947) and Gros (1954). They all agree that the incidence in females, particularly in the hypopharynx is much higher in Sweden than in Germany, Denmark, Switzerland, France and the U.S.A., and this is probably because the Paterson-Brown Kelly syndrome is common in Sweden. The female incidence of postcricoid carcinoma in this country is similar to that for hypopharyngeal carcinoma in Sweden. Thus Koszarowski states the female incidence of carcinoma in the postcricoid region in Sweden is 40 per cent., in Germany 22 per cent. and in the U.S.A. 20 per cent. The figures for carcinoma of the mesohypopharynx are—Sweden 57 per cent., U.S.A. 12 per cent. and Switzerland 9 per cent. The female incidence in this country for postcricoid carcinoma is even higher than that for cancer of the mesohypopharynx in Sweden, e.g. Christie Hospital, 1937-1958—females 85 per cent.

A follow up of many cases of the Paterson-Brown Kelly syndrome to determine the numbers who develop malignant disease has been carried out in this country by Simpson, R. (1939), Flett (1946) and Owen (1950 and

1960—personal communication). Their results vary considerably. Simpson found that 10 out of 18 cases of the syndrome developed carcinomata somewhere in the upper alimentary tract—most of them within two years of being seen. Owen followed up 28 cases for 15 years and found 5 developed postcricoid carcinoma. More recently he followed up 35 cases for 10 years and found 3 suffered malignant change. Both these series were treated with dilatation and iron therapy. Flett reported 100 cases of the syndrome seen between 1935 and 1945, none of whom had developed any malignant disease in the upper alimentary tract. Most of these cases had been followed up for less than 5 years, and Owen (1950) later reported that Flett had changed his original opinion that the condition was not pre-cancerous. Charvat (1951) reports from Poland on 30 cases of the syndrome in whom 7 per cent. developed malignant neoplasms.

What, therefore, is the incidence of malignant disease in cases of Paterson-Brown Kelly syndrome? Wynder, Hultberg *et al.* (1957) agree with Lundholme that the figure is approximately 10 per cent. Owen believes it is 15-30 per cent. and Tarle (1957) says one-third. Simpson, R. found over 50 per cent. of his cases affected.

Bonorino-Udaondo (1950), writing from South America, did not think the syndrome was pre-cancerous and Waldenstrom (1938) was critical of the papers written up to that time which suggested that it was so.

Savilahti (1946) believed that the histological changes he had noted in the hypopharynx in a post mortem on a case of the syndrome could lead to neoplastic change.

Flusser *et al.* (1954) consider that the biochemical changes in the Paterson-Brown Kelly syndrome are due to lack of iron and riboflavin for the formation of co-ferments for tissue respiration ferments. They point out that an upset of tissue respiration is one of the basic biochemical changes in malignant growths.

Finally, Simpson, R. (1939), Videbaek (1944) and author (1957) have all pointed out that the mucosa of the whole upper alimentary tract may become "pre-cancerous" so that multiple primary malignant neoplasms of the area may occur in these patients, although the hypopharynx is the site most commonly affected by malignant change.

THE PATERSON-BROWN KELLY SYNDROME

ITS RELATIONSHIP TO IRON DEFICIENCY AND POSTCRICOID CARCINOMA

PART II

A STUDY of the extensive literature on this condition (see previous article) shows that the majority of writers in recent years believe that iron deficiency is the basic cause of the syndrome. The epithelial changes in the tongue and the nails are reversible by adequate iron therapy, and there is evidence that the changes in the stomach are also reversible in young people. It seems likely that there are similar mucosal changes in the hypopharynx as a result of the iron deficiency and that the unhealthy mucosa excites an inflammatory reaction followed by fibrosis in the submucosa and even the muscular layers in this region. The mucosal changes probably occur extensively throughout the gullet, but the fibrosis is common in the postcricoid region as this is the area of maximal trauma when swallowing a solid bolus; the only area in the length of the gullet where there are skeletal elements in front and behind. As the cricoid cartilage moves upwards in swallowing, the mucosa on its posterior surface is drawn over the descending bolus and the majority of webs occur in this position.

Several important points remain in dispute.

(1) Can iron therapy and, if necessary, dilatation as well, reverse the histological changes in the hypopharynx and prevent malignant change?

(2) What proportion of patients with this syndrome will develop hypopharyngeal cancer?

(3) What proportion of patients in this country who develop postcricoid carcinoma have a preceding Paterson-Brown Kelly syndrome?

In an attempt to answer these questions, a retrospective study and follow-up has been made of cases of the Paterson-Brown Kelly syndrome seen in the Hæmatological Department of the Manchester Royal Infirmary between 1931-59, and of cases of postcricoid carcinoma seen at the Christie Hospital and Holt Radium Institute between 1937-58. Clinical and laboratory studies have also been made of 19 new cases of postcricoid carcinoma.

Survey of Cases of Paterson-Brown Kelly Syndrome

A study of 2,012 case histories of patients with hypochromic anæmia seen in the Hæmatology Department between 1931-59 showed that 106 of these patients complained of dysphagia. Ninety-four out of these

106 case histories were sufficiently detailed to allow of useful analysis. The majority of these cases were patients who attended the Hæmatology Department primarily without having been referred from other departments. These patients complained of general symptoms of anæmia, such as lassitude and dyspnœa in addition to dysphagia, and in many cases the dysphagia was of short duration (see below). A well established case of the Paterson-Brown Kelly syndrome usually gives a history of dysphagia for many years, but this is not necessary for the diagnosis as can be seen from Table III (page 550) ,where several patients with well-marked webs on barium swallow are noted as only having had dysphagia for a short time.

Duration of Dysphagia in 83 Cases

Six months or less—32 cases.
Six months-three years—30 cases.
Three-ten years—11 cases.
Ten years + —10 cases.

Therefore, the majority of patients had dysphagia for less than 3 years when first seen.

Analysis of 94 Cases of the Syndrome

Sex Incidence. Ninety females. Four males.
Age of Onset is shown per 90 cases in the histogram—Fig. 1.
Maximum incidence: Forty-Fifty years.

Associated Signs and Symptoms

All 94 cases complained of dysphagia and were anæmic. In addition, glossitis was found in 70 per cent. of the cases, koilonychia in 50 per cent., cheilosis in 38 per cent., splenomegaly in 23 per cent. Of 39 cases examined by barium swallow 19 (or 50 per cent.) showed an abnormality.

Hæmoglobin Levels

The hæmoglobin levels are shown in the following Table (all values Haldane scale).

TABLE I.
HÆMOGLOBIN BEFORE TREATMENT IN 85 CASES.

Hæmoglobin Level	No. of Cases
%	
30 or less	2
31–40	14
41–50	25
51–60	24
61–70	11
70+	9

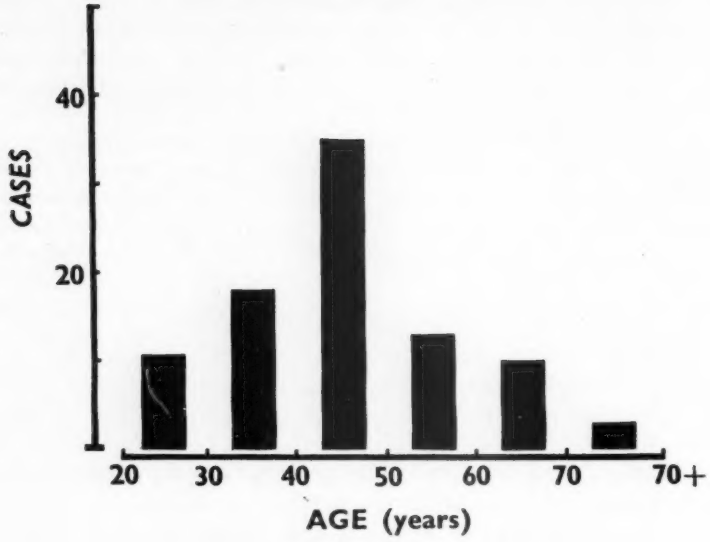


FIG. 1.

It will be seen that 60 per cent. would seem to be a critical level, the great majority of cases falling below this.

TABLE II.

HÆMOGLOBIN LEVEL WHEN DYSPHAGIA RELIEVED IN 56 CASES.

Hæmoglobin Level	No. of Cases
%	
51–60	1
61–70	5
71–80	17
81–90	15
90+	18

Table II shows the hæmoglobin level when the dysphagia was relieved, and here it will be noticed that the majority of cases had a hæmoglobin level of above 70 per cent. when relief of dysphagia occurred.

In 56 cases it was possibly to estimate the time taken to raise the hæmoglobin level to a satisfactory point and to relieve the dysphagia. In all but 9 instances this took 3 months or less, showing the rapid response of these cases to treatment.

Obvious Source of Blood Loss

In 35 out of the 94 case histories there was an obvious cause for the blood loss.

Obvious Blood Loss

Source	*No. of Patients*
Uterus	15 cases
Alimentary Tract	16 cases
Both	4 cases

Three out of the four male cases had an obvious source of blood loss from the alimentary tract. In 8 other cases there were possible contributory factors for the anæmia, viz.:

Syphilis	2 cases
Phthisis	2 cases
Rheumatoid Arthritis	2 cases
Poor Diet	2 cases

Results of Barium Swallow Examination

Thirty-nine cases had a barium swallow examination. The examination was negative in 16 cases, inconclusive in 2 and in 21 cases it was positive, showing usually a web, persistent spasm or narrowing and, in two cases, changes suggestive of carcinoma. These two cases were later proved as positive for carcinoma.

Endoscopy

Endoscopy was only performed in 15 instances. This is much lower than usual in this type of disease, but most of these cases were seen originally in the Hæmatology Department and were given the benefit of medical treatment initially. In most cases, only those who failed to respond were considered for endoscopy. In this list of 15 cases, carcinoma was discovered in two instances, webs in 11 cases and no abnormality was found on 2 occasions. In several other cases the history suggested that a web was present, but no barium swallow or endoscopy was performed.

Methods of Treatment

Except for 7 cases, all patients were treated in the first instance with oral iron, usually ferrous sulphate. Vitamin C and acid pepsin were added in some cases. No cases received Vitamin B in any form. Intravenous iron was used in the 7 cases mentioned previously and in 14 other cases which failed to respond to oral administration of iron. In 11 patients it was found necessary to perform endoscopy and dilatation. In most of these patients medical treatment was tried first, and when this failed

to relieve the dysphagia, endoscopy and dilatation were performed, usually with complete relief of symptoms.

Follow Up

There is an efficient follow up system in the Department of Hæmatology and most patients had been seen within the last 6 months. Where this

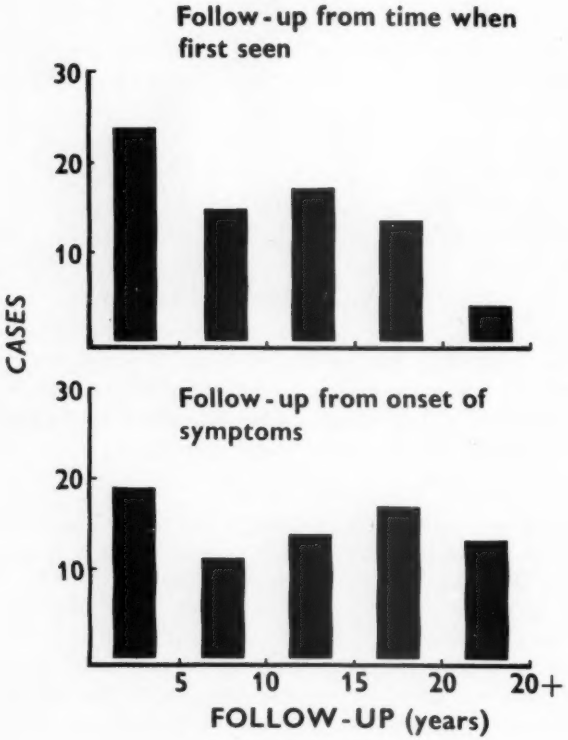


FIG. 2.

was not so they were sent a questionnaire, and if this produced no results a letter was sent to their general practitioner. By this means it was possible to follow up 73 cases to the present day.

Length of Follow Up

This is shown in the histogram (Fig. 2) as calculated:

(1) from the date of first attendance; (2) onset of symptoms.

Present Age of the Patients

Of the 73 cases successfully followed up, the present age of 34 cases is over 60 years, while 22 are between 50-60 years old, i.e. the great majority (75 per cent. approx.) are now in the age group where the development of postcricoid carcinoma is highest. (See histogram Fig. 4—page 553.)

Progress of Dysphagia

In 72 cases it was possible to assess the progress of dysphagia after treatment. Forty-three cases were symptomless, 21 of these had continued with treatment up to the present day and 18 had only had treatment in the initial stages until the dysphagia was relieved. In 4 instances it was not possible to decide whether or not they had continued with treatment.

Twenty-five cases still complained of slight symptoms. Dysphagia troubled them mainly, and they had to chew their food carefully, but they could eat a full diet. In this group 12 patients had continued with their iron therapy, 9 had only had it in the initial stages, and in 4 instances it was impossible to decide whether they had continued with treatment. In another 4 instances the dysphagia was unchanged.

Results of Treatment of Patients with Abnormal Barium Swallow

Excluding cases where the results were equivocal and two cases of proved postcricoid carcinoma, there were 19 cases with an abnormal barium swallow out of 39 cases so examined. It was possible to get a satisfactory follow up on 17 of these 19 cases. In 12 of these 17 cases the abnormality was a typical web formation in the hypopharynx, and in the remaining 5 cases there was well-marked, persistent spasm and narrowing of the hypopharynx, but without web formation.

As explained previously, most of these patients came to the Hæmatology Department in the first instance and were, therefore, treated initially with iron therapy. The results of this treatment and of combined dilatation and iron therapy are shown in the following table, first for the 12 cases with a web and then for the 5 cases with spasm. The table also shows the length of the preceding dysphagia and the period of follow-up.

The results may be summarized as follows:

Of the 12 cases with webs, 7 were treated with iron alone. In these 7 cases the preceding dysphagia had been present for an average duration of 9 months, and the average period of follow up was 5 years. The results of this treatment were that 3 remained symptom-free, 3 had slight dysphagia occasionally for solids and one case, who took iron with relief at first, had a recurrence of the dysphagia after stopping the iron and now has a well-marked web.

Illustrative of these cases is Mrs. M. F., age 46 years when first seen in 1956, complaining of breathlessness and fatigue for 18 months, dysphagia with sore tongue and mouth for 6 months. She had suffered from bleeding piles for 15 years. On examination she was an intelligent, middle-class woman of good physique and not obviously neurotic. She had angular stomatitis, glossitis and early koilonychia. The hæmoglobin was 50 per

TABLE III.

RESULTS OF TREATMENT IN 17 CASES WITH ABNORMAL BARIUM SWALLOW.

No.	Length of Dysphagia in Years	Treatment	Follow-up Period in Years	Result
12 Cases with Web.				
1	8/12	Iron only.	8	Still has dysphagia.
2	2	Iron only.	3	Slight dysphagia.
3	6/12	Iron only.	2	Symptomless.
4	4/12	Iron only.	6	Symptomless.
5	7/12	Iron only.	3	Slight dysphagia.
6	6/12	Iron only.	8	Slight dysphagia.
7	6/12	Iron only.	3	Symptomless.
8	2	Iron and dilatation.	Indeterminate	Symptomless.
9	14	Iron and dilatation.	1	Symptomless.
10	5	Iron and dilatation.	4	Slight symptoms.
11	40	Iron and dilatation.	2	Symptomless.
12	8	Iron and delayed dilatation 18 months later.	2	Symptomless.
5 Cases with Spasm.				
13	1	Iron only.	12	Symptomless.
14	1/12	Iron only.	12	Symptomless.
15	20	Iron only.	11	Symptomless.
16	5	Iron only.	16	Repeated relapses: (persistent menorrhagia.
17	1	Iron with dilatation.	4	Symptomless.

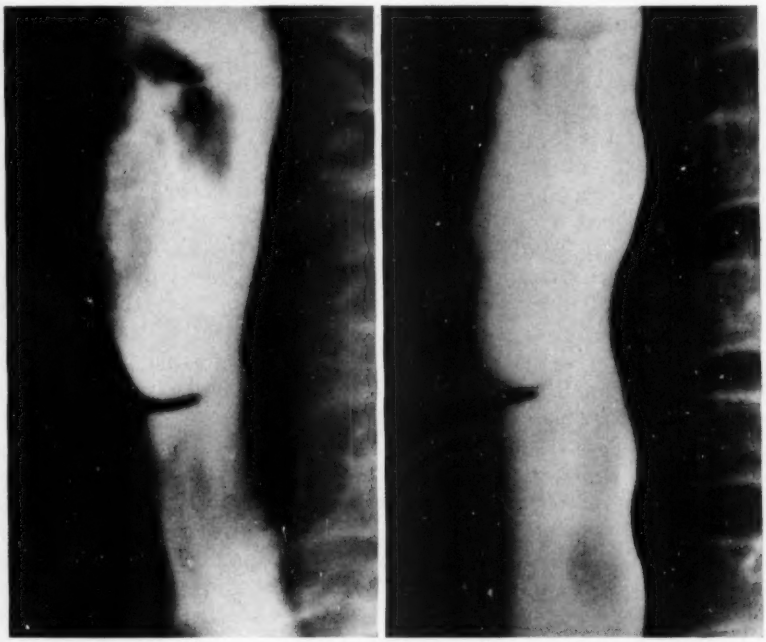
cent., colour index 0·53. A fractional test meal showed achlorhydria. A barium swallow showed a well-marked web. (Fig. 3a below.)

She was treated with oral iron and after 3 months' treatment the hæmoglobin was 85 per cent. and the dysphagia completely relieved. Hæmorrhoidectomy was performed in 1958. At no time did she have an endoscopy nor dilatation. When seen personally in July 1960 she looked well and, in spite of considerable family worries, was eating a full diet at normal speed. The angular stomatitis, glossitis and koilonychia had recovered completely. The hæmoglobin was 94 per cent. The barium swallow, however, still showed the web, although it appeared slightly smaller. (See Fig. 3b.)

In the 4 cases treated by iron therapy and immediate dilatation, the average length of time for preceding dysphagia was 15 years and the

average follow up period 2 years. Three of these cases obtained complete relief of symptoms and one case continued to have slight dysphagia.

Finally, one case with three webs on X-ray was treated initially with iron alone. All the symptoms except dysphagia were relieved. Eighteen months later dilatation was performed and she has remained symptom-free now for 2 years.



A. B.

FIG. 3.

In the 5 cases with spasm, the average time for the preceding dysphagia varied considerably, in one case being 20 years, but excluding this case, it was $3\frac{1}{2}$ years. The average follow up period has been 11 years. Four of these cases had iron alone, 3 with complete relief of symptoms. The fourth case has had several relapses, probably due to persistent menorrhagia. One of the cases was treated with iron therapy and dilatation and has remained symptomless for 4 years.

The number of these cases is small, but the results of treatment suggest that even cases, where a web is shown on X-ray, will respond to iron therapy alone, providing the dysphagia has not been present for more than a year or two and that presumably the histological changes in

the hypopharynx are not too advanced. Where the dysphagia has been present for many years, dilatation of the web will be required as well as iron therapy.

Finally, cases with spasm in the hypopharynx will probably respond satisfactorily to iron therapy alone.

Incidence of Neoplasms

In 76 cases it was possible to decide whether or not the patient had developed a neoplasm up to the present day or to the time of death.

As shown previously (see Fig. 2) approximately half the patients have been followed up for more than 10 years from the date of their first attendance and for more than fifteen years from the onset of dysphagia. Three-quarters of them are now over 50 years old and in the age group where the incidence of postcricoid neoplasm is highest. In one case the patient developed a postcricoid neoplasm after ten years' dysphagia. She was first seen, aged 57 years, in 1953 complaining of dysphagia for 3 years. Oral iron therapy only partially relieved her symptoms and the treatment lapsed. In 1958 she developed a carcinoma of the lip which was treated, apparently successfully, by external irradiation. Renewed iron therapy improved her swallowing temporarily, but in 1960 she presented with 3 months' increased dysphagia and was found to have an extensive postcricoid carcinoma.

Two other cases also proved to have postcricoid neoplasms. One, a male aged 58 years, attended with dysphagia and anæmia of 5 weeks' duration. Iron therapy for 3 months produced no improvement and further investigation showed the neoplasm. The other case was a woman aged 63 years, with a 5 weeks' history of dysphagia. She was diagnosed as having a carcinoma and treated successfully, but later developed a carcinoma of a salivary gland and died. In neither of these cases was there a history of preceding Paterson-Brown Kelly syndrome and the anæmia and dysphagia were probably due to the carcinoma in the first instance.

Apart from these three, one case developed an œsophageal neoplasm after a period of 2 years and there was one case each of neoplasm in the larynx, the stomach and the colon, while another patient developed lymphatic leukæmia.

Retrospective Study of Cases of Postcricoid Carcinoma

In the period 1937-58 a total of 322 new cases of postcricoid carcinoma was seen at the Christie Hospital and Holt Radium Institute.

Sex Incidence. Of these 322 cases, 272 were women (i.e. 85 per cent.) and 50 were men (i.e. 15 per cent.). This is a reversal of the usual sex incidence for carcinoma in the upper alimentary and respiratory tracts as shown in the following table:

TABLE IV.

SEX INCIDENCE AS PERCENTAGES IN CARCINOMATA UPPER ALIMENTARY TRACT, 1945-56. (CHRISTIE HOSPITAL.)

Site	Total No. of Cases	% Males	% Females
Mouth	2,390	73·6	26·4
Pharynx	1,696	63·3	36·7
Larynx	953	88·4	11·6
Œsophagus	405	72·6	27·4
Postcricoid (1937-58)	322	15·0	85·0

Age Incidence. This is shown for males and females separately in the following histogram (Fig. 4).

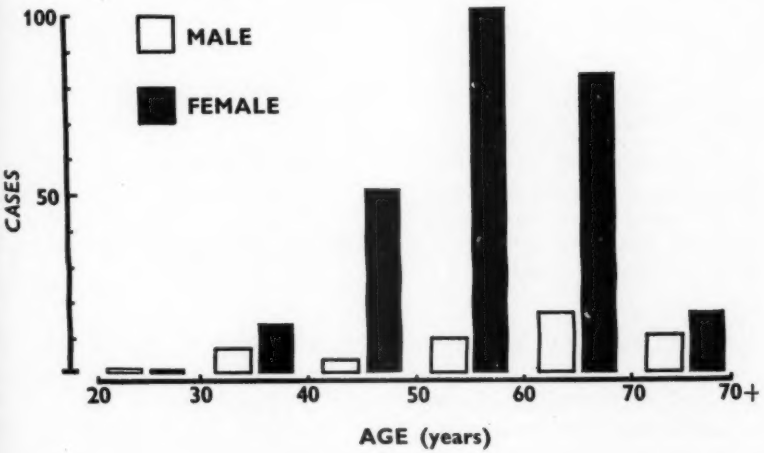


FIG. 4.

The peak age incidence for women is 50-60 years and that for men 60-70 years. The majority of cases of Paterson-Brown Kelly syndrome first present between 40-50 years. (See Fig. 1.)

Ætiological Factors

Incidence of Preceding Paterson-Brown Kelly Syndrome

The reversal of the usual sex incidence for carcinomata of the upper alimentary tract which is seen in the postcricoid region is usually attributed to the presence of a preceding hypopharyngitis; part of the Paterson-Brown Kelly syndrome which occurs predominantly in women.

The case notes of the 322 cases were studied in detail for ætiological factors and particularly for evidence of Paterson-Brown Kelly syndrome preceding the development of the cancer. The notes have been examined critically from this point of view and the presence of a previous Paterson-Brown Kelly syndrome has been classed as either "obvious", "probable" or "possible". The obvious cases were those in which the full syndrome was present. The "probables" had hypochromic anæmia or all the stigmata with a long history of dysphagia, and the "possibles" had some of the stigmata or a long history of dysphagia or hypochromic anæmia. The number of cases in each group is given in the Table below, and if all are included, the total is 99 out of 322 cases or approximately 30 per cent.

TABLE V.

Obvious	Probable	Possible
18	21	60

Other Ætiological Factors

In 9 cases there was a history of previous irradiation of the neck for thryotoxicosis. Another 6 cases had a history of macrocytic anæmia. In one case there was a history of swallowing caustics, in another of syphilitic infection, and in a third there was widespread leukoplakia in the mouth and pharynx.

Study of Recent Cases of Postcricoid Carcinoma

During the past 18 months it has been possible to study 19 new cases of postcricoid carcinoma: all were females. In most cases it was possible to perform laboratory tests to estimate the hæmoglobin, serum iron and iron binding capacity values. In addition, sternal puncture was performed and the marrow examined for hæmosiderin in an attempt to estimate the state of the patient's iron stores.

As a control, the same examinations, both clinical and laboratory, were performed on five female patients with other types of malignant disease and on another nine female patients chosen at random from those admitted to the Ear, Nose and Throat Ward. All these control patients were in a similar age group to that of the cases of postcricoid carcinoma.

The results of these examinations are given in Table VI.

As can be seen there was a high incidence of preceding dysphagia and koilonychia, cheilosis and glossitis in the group of new cases of postcricoid carcinoma as compared with the controls. The serum iron level was also considerably lower in the cases of postcricoid carcinoma, but as

most patients with malignant disease have low serum iron levels, this finding may not be significant.

In regard to a history of previous abnormal blood loss and anæmia there was no great difference between the two groups. Similarly both groups showed total serum iron binding capacity levels above the normal values and a lack of hæmosiderin in the marrow specimens. The writer

TABLE VI.

NEW CASES OF POSTCRICOID CARCINOMA. CONTROL SERIES.

	Total 19 cases	Total 14 cases
Dysphagia for longer than 5 years.	11 cases.	0
Glossitis, Cheilosis and Koilonychia.	8 cases.	1
Hæmoglobin level below 80 per cent.	4 cases.	2
History of previous abnormal blood loss.	11 cases.	6
History of previous anæmia.	7 cases.	4
Average serum iron level.	54 microgrammes per 100 cc.	100 microgrammes per 100 cc.
Average level of serum iron binding capacity.	330 microgrammes per 100 cc. in 15 cases.	395 microgrammes per 100 cc. (in 13 cases).
Hæmosiderin content of the marrow.	Only one specimen showed normal quantities. Hæmosiderin absent or grossly reduced in remainder.	Grossly reduced or absent in all specimens.

believes this is further evidence of how common these disorders are amongst the adult female population in this country.

To sum up the findings, there was strong evidence of a preceding Paterson-Brown Kelly syndrome in seven cases and some signs of it in a further six cases, giving a total of 13 out of 19 cases. Thus, two-thirds of the cases may be suspected of having this syndrome as compared to the one-third who were deduced to have it from a retrospective study of 322 case notes (see above). The number of recent cases is too small for any concrete deductions to be made. However, it is probable that the figure of one-third in the retrospective study is too low.

Discussion

A review of the literature suggests that an iron deficiency is the basic cause of the Paterson-Brown Kelly syndrome. Several writers (Owen (1950), Tarle (1957), Wynder *et al.* (1957)) claim that between 10 per cent. and 30 per cent. of these patients will develop a cancer somewhere in the upper alimentary tract, the commonest site being the postcricoid area.

Studies of cases of hypopharyngeal carcinoma in Sweden show that a high proportion have a preceding Paterson-Brown Kelly syndrome.

The present study shows that between one-third and two-thirds of the cases of postcricoid carcinoma treated at the Christie Hospital and Holt Radium Institute in the past thirty years had a preceding Paterson-Brown Kelly syndrome.

Of 76 cases of the Paterson-Brown Kelly syndrome treated in the Hæmatology Department of the Manchester Royal Infirmary, and followed up for periods of up to twenty-five years, only one developed a postcricoid carcinoma, and this in spite of three-quarters of these patients now being over 50 years old. The majority of these patients had dysphagia for less then three years before being treated. Most were treated with iron only and their symptoms were usually relieved within three months of commencing treatment. When dysphagia was longstanding, dilatation was also necessary. All were carefully followed up and their iron deficiency efficiently treated. The low incidence of postcricoid carcinoma developing in these patients may be due to:

(a) the short duration of the preceding dysphagia.
(b) efficient treatment, especially in correcting the iron deficiency.

There is evidence in the literature that the histological changes in the mouth and nails can be corrected by iron therapy. The changes in the stomach may well be reversible, too, in young people. It seems reasonable to suppose that such a return to normal may be possible in the mucosa of the hypopharynx, particularly where such changes are of recent origin, but the underlying fibrosis in the submucosa, and sometimes present also in the muscular layers, is unlikely to change, even though the stricture be dilated successfully. Postcricoid carcinoma develops in the mucosa so that reversal of the histological changes there might well prevent the development of malignant change. Holmgren (1943) and Lindvall (1953) point out that postcricoid carcinoma often develops above the site of a pre-existing web and they suggest that irritation due to food stasis may be an important factor. If this is true, then obviously dilatation of the stricture, to prevent such stasis, is also of prime importance in preventing malignant change.

Unfortunately, many cases of postcricoid carcinoma who show evidence of preceding Paterson-Brown Kelly syndrome have never sought medical advice, have patiently endured considerable dysphagia for many years, or, having sought advice, they have been treated ineffectively or not carefully followed up. For these reasons, treating the condition once it is established will never be as effective in reducing the incidence of postcricoid carcinoma as preventive treatment aimed at eradicating the state of chronic iron deficiency so common amongst adult females in this country Davidson *et al.* (1938) estimated that up to 50 per cent. of the female

population in the childbearing period of life had some degree of hypochromic anæmia. While the diet of most classes in this country has improved since the last War, the use of aluminium cooking utensils has reduced the intake of "incidental" iron.

In Sweden and the United States of America the flour used in bread-making is fortified with iron. This form of "forced" iron therapy is likely to be particularly effective in this country amongst women in the poorer classes where the incidence of iron deficiency is highest, because tea and bread and margarine often form a large part of their diet.

Sweden introduced iron into the bread in 1940 and the following Table shows the striking reduction in the incidence of cases of hypopharyngeal carcinoma seen at the Radiumhummet (Stockholm) some twenty years later (Folke-Jacobson—personal communication).

TABLE VII.

CARCINOMA OF THE HYPOPHARYNX (RADIUMHUMMET).

	Male	Female	Total
1935	14	22	36
1936	15	16	31
1937	23	23	46
1958	14	6	20
1959	7	9	16

There is no such reduction occurring in the number of new cases of postcricoid carcinoma seen at the Christie Hospital and Holt Radium Institute.

New Cases of Postcricoid Carcinoma (Christie Hospital and Holt Radium Institute)

1940-48 inclusive	Total 164 cases
1950-58 inclusive	Total 154 cases

If this trend is maintained in Sweden, it would provide a strong argument in favour of the adoption of iron fortified bread in this country.

Summary

A review of the literature suggests that cases of Paterson-Brown Kelly syndrome are to be found in most European countries and in North and South America.

The probable basic cause is iron deficiency which markedly affects the health of the mucosa of the upper alimentary tract in some people.

In cases where the dysphagia is of relatively short duration, efficient

iron therapy and control of any source of excessive blood loss can often relieve the symptoms, usually within three months. Where the dysphagia has been present for two years or longer dilatation will probably be necessary in addition to the iron therapy.

A long term follow up on 76 cases of the syndrome treated in this way shows that only one developed a postcricoid neoplasm.

A survey of the records of 322 cases of postcricoid carcinoma and a clinical and laboratory study of 19 new cases of the disease suggests that between one-third and two-thirds of such cases have a preceding Paterson-Brown Kelly syndrome.

The possibility of preventing malignant change occurring in cases of Paterson-Brown Kelly syndrome by effective treatment is discussed. It is argued that preventive treatment by fortification with iron of the flour used in breadmaking would be the most effective method of reducing the incidence of postcricoid neoplasm in this country.

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Mr. Robert Owen has been very generous and kind in giving me the benefit of his unrivalled experience and knowledge of this condition.

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APPENDIX I.

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THE METABOLISM OF THE COCHLEAR AND VESTIBULAR END-ORGANS*

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THE metabolic processes concerned with the function of the sensory end-organs of the cochlea and the vestibule depend on a number of factors. They include the chemical composition of the various component parts of the sense-organ, and of their electrical state during resting periods and during activity. They also include the richness or poverty of the blood-supply and the availability of adequate oxygen.

In each of the separate sense-organs the hair-cells are the sensorial units, where transduction of mechanical movement into nerve stimulation takes place. In each case the hair-cells are surmounted by a so-called "gelatinous mass" into which the hairs of the sensory cells project. The whole is surrounded by the endolymph, enclosed in a membranous tube which is just large enough to contain the sense organ. This tube is enclosed in a bony tube of much greater calibre which is filled with perilymph.

The actual transduction of mechanical energy into neuro-electrical activity depends on the relative movement between the hair-processes of the sensory cells and the gelatinous mass which is superimposed upon them and, in part at any rate, encloses them. The chemical composition and the electrical state of the hair processes and of the gelatinous mass are all important for the progress of this transduction. Whether the gelatinous mass is described as the tectorial membrane, the otolith membrane or the cupula makes no real difference. In each part of the inner ear the relations are the same and in each case the nerve impulse depends on the movement of one of these structures relative to the other.

In the cochlea the endolymph is separated from the perilymph by the basilar membrane with the large cuboidal cells of Claudius, and by Reissner's membrane, which is usually one cell in thickness but may occasionally be two or more cells thick. This is probably due to persistence of the embryonic mesodermal backing of the endodermal layer of the membrane. The endolymph is separated from the structures of the sense organ by the reticular membrane which is electrically and chemically impermeable. In the utricle, saccule and semicircular canals the endolymph and

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perilymph are separated by the wall of the membranous labyrinth which is one or two cells in thickness.

The composition of the perilymph is comparable to that of the cerebrospinal fluid. The proportions of sodium, potassium, calcium and magnesium are the same, as is also that of the chlorides. It has been shown by Citron and Exley (1957) that in mammals—the guinea-pig and especially the cat—the protein content is higher in the perilymph than in cerebrospinal fluid. The proportion is 3:1 in the guinea pig and 6:1 in the cat. The non-protein nitrogen content of the two fluids is practically identical. In many animals there is a communication between the perilymph and the cerebrospinal fluid but in man this communication appears to be closed.

The endolymph differs in its composition from that of the perilymph in many important characteristics—in its content of protein and of electrolytes, and also of the mucopolysaccharides. These are discussed under each of the three headings.

Rauch (1960) has established, by means of his freezing method, that the fluid in the tunnel of Corti—which lies between the basilar and the reticulated membrane—has not the same composition as endolymph. It resembles perilymph in the proportion of its constituents except that there is slightly less protein.

Protein

In the cat the protein in the endolymph is rather less than half that of the perilymph (Ledoux, 1941), in the guinea-pig it is one-third the amount (Citron and Exley, 1957) but in the piked dog-fish (Acanthias) the amount of protein in the endolymph is fifty per cent. more than in the perilymph (Vilstrup and Jensen, 1954) though the total nitrogen is slightly higher in perilymph than in endolymph. According to Citron and Exley the amounts of non-protein nitrogen in the guinea-pig is the same in endolymph and perilymph.

It has been shown by Rauch that the amount of protein in these fluids in the human subject is as follows—cerebrospinal fluid 15-25, perilymph 75-100, endolymph 10 mg. per 100 ml. He has also shown that the proportion of protein in cerebrospinal fluid varies according to the position in the cerebrospinal system at which it is examined. He has found that in the ventricles of the brain there is 0·05 mg./100 ml., in the cisterna basalis 1·0 mg./100 ml. and at the lower end of the spinal theca it is even higher—12-20 mg./100 ml.

Vilstrup and Jensen have shown that the proteins in the endolymph are wholly globulin, whilst in the perilymph one-fifth of the protein is albumen. In human serum the proportions are reversed, four-fifths albumen and one-fifth globulin. In the vitreous body of the human eye

the albumens and globulins are nearly equal. The proportions of the three types of globulin are as follows:

	Endolymph	Perilymph
α Globulin	10·5	7·5
β Globulin	23·5	26·0
γ Globulin	65·0	46·0

Meyer zum Gottesberge (1960), by applying autoradiographic technique and using radioactive Tritium-Leucine in guinea-pigs and pigeons, has been able to demonstrate protein activity of varying degrees of intensity in different parts of the cochlea. The ganglion cells in the spiral ganglion and in the nuclei in the hind brain were strongly impregnated. The hair cells, and also their supporting cells in the organ of Corti showed intense protein activity, equally on the inner and on the outer sides of the rods of Corti. The stria vascularis also indicates active protein metabolism, but there was no evidence of radioactivity, and therefore no evidence of protein metabolism in the tectorial membrane. Plester (1960) working with Meyer zum Gottesberge has shown that there is protein metabolic activity in Reissner's membrane, and considers that this is evident because of the difference in potential of 80 or more milli-volts, between the fluids on its two sides—the perilymph of the scala vestibuli and the endolymph of the scala media.

Wislocki and Ladman (1955) have shown that there is a considerable amount of protein in the tectorial and otolith membrane in mice and the human fœtus, and that some of the protein consists of cystine associated with disulphide.

Bélanger (1956) injected radioactive sulphur-protein compounds (methionine) into young rats, but found that the tectorial and otolith membranes and cupulae did not take up these substances.

Electrolytes

There is a considerable variation in the endolymph content of electrolytes in guinea-pigs, cats and man. Whereas in serum, cerebrospinal fluid and in perilymph the sodium content is many times that of potassium, in the endolymph this proportion is reversed—the potassium content being as much as seven times that of the sodium. This is explained by the fact that the actual amount of potassium is greatly increased and that of sodium greatly decreased in the endolymph. This preponderance of potassium is comparable to that of intracellular protoplasm, but is found in no other extra-cellular fluid. These proportions have been demonstrated in guinea-pigs and in cats by Ledoux (1950) and by Citron and Exley (1957), and in the human ear by Rauch (1960), who has shown that the proportion of potassium and sodium in the human endolymph resembles closely that of the other mammals examined. He has demonstrated,

working with Wullstein and Kley (1960), that endolymph, withdrawn from the basal turn of the cochlea and from the utricle of human subjects who were being operated upon for intractable Ménière's symptoms, contains the same relative proportions of potassium and sodium as the endolymph of the normal ear.

In the endolymph, magnesium is found in about half the amount in which it is present in cerebrospinal fluid and in perilymph, whilst chlorides are slightly less in the endolymph than in the other two fluids. Vilstrup and Jensen (1955) have stated that in the dog-fish endolymph the disproportion between the amounts of potassium and sodium is less than in mammals.

The mucopolysaccharides

The presence of mucopolysaccharides was demonstrated in the tectorial membrane of the rat by Bélanger (1953) by injecting radioactive sulphur (S^{35}) and employing the technique of autoradiography. The same technique has been employed by Dohlman and Ormerod (1958-59-60) in the pigeon and the course of the radioactive sulpho-mucopolysaccharide has been followed from the tegmentum vasculosum and from the planum semilunatum through the endolymph to the tectorial membrane, otolith membrane and cupula. Such sulphur compounds could be identified in the secretory membrane within half an hour of injection and they reached the gelatinous mass in not more than four hours. They apparently slowly leave this tissue and pass through the endolymph along the ductus endolymphaticus whence they are re-absorbed through the surrounding tissues back into the blood stream. There are traces in the tectorial membrane, and cupula for periods up to thirty days, suggesting that the mucopolysaccharide plays an important part in the function of the gelatinous masses. At no period during this cycle was there any significant evidence of sulpho-mucopolysaccharides in any of the areas of sensory epithelium.

Jensen (1954) and Vilstrup and Jensen (1954) have demonstrated that there is a considerable amount (73 mg./100 ml.) of mucopolysaccharide in the endolymph of the selachian dog-fish (Acanthias), but they were not able to demonstrate it in the perilymph. They have however been able to demonstrate in elasmobranch fishes such as the cod, that the reverse occurs and that there are mucopolysaccharides in the perilymph but not in the endolymph. This may be connected with the swift movements and quick turning of the selachians and the relatively slow motions of the cod and similar fishes.

Citron and Exley (1957) and Poulsen (1959) have demonstrated that there are mucopolysaccharides in both the endolymph and the perilymph of the guinea-pig. Dohlman and Ormerod found that in the pigeon the sulpho-mucopolysaccharides were present in significant amounts only in the endolymph.

Poulsen (1959) and Jensen and Vilstrup (1960) have shown also that the proportion of mucopolysaccharide is greater in the perilymph of the superior parts of the labyrinth—the cochlea and saccule—than in the inferior parts—the utricle and semicircular canals—of the cod fish. They are of the opinion also that all the mucopolysaccharide in the superior part of the cod's labyrinth is hyaluronic acid.

In Italy, Jurato (1960) discussed the presence of mucopolysaccharides in the tectorial membrane. He quotes Pusateri Santi (1950), G. and E. Zorzoli (1953) and Ferreri and Crifó (1956) who by histochemical methods have demonstrated these substances in the tectorial membrane. The Zorzolis have also detected mucopolysaccharides in the sensory cells of the maculae of the utricle and saccule and of the crista of the three semicircular canals.

It has been shown that the appearance of the endolymph in the selachian fishes is similar to that of the vitreous body in the eye—a viscid semi-solid mass. It has been shown to consist of a solution of hyaluronic acid, and liquefies rapidly in the presence of hyaluronidase. The viscosity of this endolymph is probably greater than that in small mammals and this may be due to the different chemical nature of the mucopolysaccharide concerned. The viscosity tends to be greater in the endolymph than in the perilymph of the dog-fish—due to the greater amount of mucopolysaccharide, and it has been presumed that this viscosity has some damping effect on what could otherwise be too violent oscillations of the endolymph.

A viscous fluid of this nature also has a quality known as flow-elasticity. An elastic fluid can move through short distances, without great loss of energy; the energy may be stored as a "elastic potential" and after a variable time this energy will become kinetic and the fluid will flow to its starting point—the elastic recoil.

The mucopolysaccharide molecule is a very heavy and elongated one. Its molecular weight may be as much as one million and the molecular thread as much as 0·5 μ in length. It has been suggested (Jensen, Christensen, Koefoed and Vilstrup, 1954, 1955 and 1959) that when a solution of mucopolysaccharide flows even for a very short distance along a narrow space, that the molecules, of which one end becomes adherent to the walls of the space, are bent and this gives rise to a change in potential—an increase in positive charge at the leading portion of the fluid and a decrease at the trailing portion. This change in potential is known as the "flow potential" and persists, with the elastic potential until the elastic recoil brings the fluid back to its starting point.

The Stria Vascularis

The stria vascularis has generally been accepted as the source of the various constituents of endolymph, and similar structures in the walls of

the other parts of the membranous labyrinth appear to have the same function. If the perilymph is not derived from the choroid plexuses and the cerebrospinal fluid, nor by transudation through Reissner's membrane it must be produced from the walls of some other part of the labyrinth.

The electric potentials of the inner ear vary very much. That of the endolymph in the scala media is strongly positive compared with the potential of the perilymph in the scala vestibuli, but the difference is less marked in other parts of the labyrinth, as shown by Catherine Smith, Lowry and Wu (1954). The potential of the perilymph in the scala vestibuli is slightly positive compared with that of the scala tympani, but that of the cells of the organ of Corti, like other intracellular matter, is strongly negative. The electric potential on the surface of the stria vascularis has been shown to be strongly positive as in many other secretory membranes, and it has been assumed to be the source of the high positive potential of the endolymph (Békésy, 1952; Davis, 1958; Tasaki, 1954.)

Trincker (1959) has shown in the ampullae of the semicircular canals that as in the cochlea, the potential of the endolymph is positive as compared with the perilymph, and strongly so compared with the crista and with the vestibular nerve fibres.

Investigations of the metabolic activity in the stria vascularis and other parts of the cochlea have been carried out by Vosteen, by Rodgers, Chou and Hughes and by Meyer zum Gottesberge. Vosteen has used the method of measuring respiration in the tissues by staining techniques to distinguish the respiratory enzymes—succinodehydrogenase, cytochromoxydase and diaphorase. He found the greatest activity in the stria vascularis, in the spiral ligament immediately behind the external sulcus and to a less extent in the hair-cells.

Rodgers, Chou and Hughes have measured the metabolic activity, by determining the rate of oxygen uptake by the tissue concerned in the presence of organic substrates, using the Cartesian diver technique. They found that there was great activity in the stria vascularis which had a respiration rate approximately ten times that of the liver from the same animal. In almost every experiment the rate of respiration of the spiral ligament was negligibly low. Both, they and Vosteen have demonstrated the large number of mitochondriae in the cells of the stria vascularis, and they have noted that there were relatively few mitochondriae in the spiral ligament.

Meyer zum Gottesberge has shown by his method of radioactive tritium-leucine autoradiography that there is intense protein metabolic activity in the stria vascularis of the guinea-pig, but somewhat less in the tegmentum vasculosum of the pigeon.

The very considerable total metabolic activity in the stria vascularis, and tegmentum vasculosum, as shown by a variety of techniques—histochemical, biological, autoradiographic and electrical, confirm the

opinion that the endolymph and its constituents are secreted in these structures.

It has been demonstrated that the enzyme, carbonic anhydrase, which has been identified in the ciliary body and in the choroid plexus, plays some part in the secretion of the aqueous humour and the cerebrospinal fluid. This has led Erulkar and Maren (1961) to investigate the likelihood of similar activity in the stria vascularis and other parts of the inner ear. They injected the specific inhibitor—acetazolamide (Diamox) intravenously into a number of cats. The animals suffered from a metabolic acidosis and the plasma content of carbon dioxide was reduced. Preliminary results for the endolymph show that the chlorides tended to decrease, those of the perilymph becoming proportionately, if not actually, greater.

The usual very high content of potassium was not found in the endolymph after injection of acetazolamide. The amount of potassium in the perilymph and cerebrospinal fluid did not differ from that in control animals. The experiments denote that following injection of the enzyme inhibitor there is a diminution of tissue respiratory activity which shows itself in the endolymph by a very marked reduction in the amount of potassium.

Vosteen (1960) and Rodgers, Chou and Hughes (1960) have demonstrated the high degree of respiratory activity in the stria vascularis and these further results by Erulkar and Maren appear to confirm that the unusually great amount of potassium in the endolymph is secreted by the stria vascularis.

Reissner's Membrane

Reissner's membrane consists of a single layer of somewhat flattened cells which do not suggest any secretory or even metabolic activity. Introduction of radioactive sulphur has not demonstrated mucopolysaccharide metabolism in this membrane (Dohlman and Ormerod, 1960) but Plester (1960) has shown by using radioactive tritium-leucine that there is a slight protein metabolism in the cells of Reissner's membrane. The autoradiographic record of this activity is much less marked than that recorded in the stria vascularis or in ganglion cells connected with the inner ear. Plester suggests that the considerable difference of electric potential between the two fluids on either side of the membrane may give rise to the somewhat slight metabolic activity demonstrated in Reissner's membrane. Rauch (1960) has demonstrated in the guinea-pig by his freezing methods that there is a slight difference in the electrolyte and the enzyme contents in the perilymph of the scala vestibuli and that of the scala tympani especially in the first basic turn. He suggests that there may be a slight transudation across Reissner's membrane from the endolymph to the perilymph of the scala vestibuli, which accounts for

this small variation, but he does not consider that there is evidence of a metabolic change such as would explain the great difference between electrolyte contents of the endolymph and perilymph.

The Tectorial Membrane

It has been shown by Hardesty in 1911 and by Prentiss in 1913 that the tectorial membrane does not consist of a homogeneous gelatinous mass, but that it has a honeycomb appearance, due to a great number of interlacing fibrils which divide the structure into channels and chambers, filled with a fluid resembling endolymph. They considered that the physical and anatomical conditions were such as would be expected if the tectorial membrane was functional in transmitting sound energy to the hairs. More recent anatomical examination has confirmed these findings, and by electron-microscopy the tectorial membrane and the cupula are seen to contain a great number of fine tubular spaces which begin opposite to the hair bearing surface of the sensory cells and it is possible to detect the hair processes passing through the sub-tectorial or sub-cupular space to enter into these tubular spaces.

In the otolith membrane and in the cupula, and therefore in all probability in the tectorial membrane also, the movement is relative to the comparatively fixed sensory epithelial structure.

As has been shown by Vilstrup and Jensen, Koefoed and others, the movement of a solution of hyaluronic acid and presumably of other similar polysaccharides along a tube in one direction gives rise to a change of potential in one sense and that movement of fluid in the reverse direction gives rise to a change of potential in the opposite sense. The insertion of a negatively charged hair process into a space in the tectorial or other membrane, filled with such a solution and with a strong positive charge, will by induction give rise to an increase in the negative charge in the hair-process and therefore to an increased negative charge at the nerve end of the cell. Movement of the hair processes in and out of the spaces in the various gelatinous membranes will therefore give rise to changes, in opposite directions, of the electrical potential in that part of the cell which is in intimate contact with the nerve endings and thus to set up action potentials in the nerve elements.

Summary

During the past decade there has been added by many workers in many countries, much detail about the biochemical and physiological properties of the structures making up the various sense organs and of the fluids of the inner ear. Such information may be epitomized in a few sentences under these different headings.

Stria vascularis

Respiratory exchanges, mucopolysaccharide and protein metabolic activity very high. High positive electric potential on surface. Rich blood vessel supply.

Tectorial membrane

High mucopolysaccharide activity. Protein content but not active metabolism. High positive electric potential. Respiratory exchanges almost absent. No blood vessel supply.

Reissner's membrane

Slight protein metabolic activity.
No noticeable mucopolysaccharide activity.
No noticeable respiratory exchanges.
No blood supply.

Sensory cells of organ of Corti, of crista and masculae

High protein metabolic activity. Practically no mucopolysaccharide activity. Negative electric potential. Respiratory exchanges marked. Moderate blood vessel supply.

Endolymph

High potassium content.
Low sodium content.
Low magnesium content.
Low protein content.
High positive electric potential.
Variable mucopolysaccharides in different species of animals.

Perilymph

Low potassium content.
Relatively high sodium content.
High protein content compared with endolymph or cerebrospinal fluid.
Negative electric potential compared with endolymph.
Variable mucopolysaccharide according to species.

The composition of the labyrinthine fluids in the human ear may be compared with that of the cerebrospinal fluid and plasma in the human subject in the following table.

From the accumulated knowledge about the various parts of the inner ear it may perhaps be accepted that, because of its rich respiratory

exchanges and its protein metabolism, the stria vascularis has a high metabolic purpose. In addition to this its rich blood supply indicates its probable secretory function and the high mucopolysaccharide activity which, besides being part of the secretory function, may be concerned with the mounting of the high positive electric potential.

	Plasma*	C.s.f.	Perilymph	Endolymph
Protein ..	6,000–8,000	10–38	75–100	10
K	20	12–17	15	140
Na	140	150	148	26
Cl_2	600	750	120	110
Sugar	70–120	40–80		
Magnesium ..	1·0–3·0	2·0	2·0	0·9
Ca	7·0	3·0	3·0	3·0

*cf. Flexner

The tectorial and otolith membranes and cupulae with no protein metabolic activity have no secretory function. Their strong affinity for mucopolysaccharides and retention of these substances are probably concerned with the maintenance of the high positive electric potential, which is necessary for the transduction of sound into nerve impulse.

The sensory epithelium in the various parts of the inner ear has no appreciable mucopolysaccharide activity and does not maintain a positive electric potential. It shows marked respiratory exchanges and high protein metabolic activity and at the same time has only a moderately rich blood supply. The properties identified and described explain its transductory and therefore sensorial function.

The purpose of the unexpectedly high potassium content in the endolymph, which seems to be produced by the stria vascularis, is to maintain the positive electric potential or to provide a medium in which it can be maintained.

Finally, and arising from these facts a suggestion is put forward as to how mechanical energy reaching the various sense organs is converted into afferent nerve impulses.

Epilogue

Much experimental and clinical evidence as to the influence of the cervical sympathetic nervous system on the blood supply and secretory activity of the cochlea has recently been furnished by Seymour (1960) and Golding-Wood (1960).

Constriction of the vascular supply and consequent anoxia of the stria vascularis is said to result in a reduction of the amount of endolymph secreted and therefore a partial collapse of the scala media. This

is followed, when degenerative processes have taken place, by an increase in the endolymph mass and a distension of the scala media.

It might be expected that the fluid in a distended scala, following the degeneration of the secretory epithelium, would present some abnormalities in its chemical composition, but Rauch, with Wullstein and Kley, have demonstrated the normal human composition of the endolymph from the basal coil of the cochlea and from the utricle in cases in which the Ménière condition was severe and protracted enough to lead to destructive surgery.

It is suggested that changes in the sympathetic nervous system are responsible firstly for the reduction and later for the increase in the amount of endolymph. It is noteworthy that collapse, and dilatation of the scala media occur in the different varieties of Scheibe's type of congenital deafness, and that dilatation also occurs in cases of syphilitic congenital deafness, Ormerod (1960). This dilatation is also seen in cases of labyrinthitis associated with otitis media and also with various types of meningitis, Fraser (1922, 1932).

There can be little doubt that the cervical sympathetic nervous system has an influence on the vessels of the inner ear and therefore on its blood and oxygen supply. It is not, however, so certain that the somewhat complex biochemical composition and metabolic behaviour of the sense organs are controlled by this system.

It has been demonstrated anatomically, by Rasmussen, Portmann, Schuknecht and others that there are efferent fibres in the cochlear nerve with appropriate nerve endings in the sensory epithelium. Dohlman, Farkshidy and Salonna have shown that efferent fibres are similarly present in the vestibular nerve and sense organs. It is possible that some degree of control of the metabolic processes of the inner ear is exercised by these efferent fibres and therefore by the parasympathetic system. It may be that further investigation of the physiology of this system may throw light on the working of the inner ear and help to elucidate some of the problems.

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HISTOPATHOLOGICAL AND HISTOCHEMICAL STUDIES ON ATROPHIC RHINITIS

By MILES TAYLOR and AUSTEN YOUNG (Sheffield)

Introduction

ATROPHIC rhinitis is a chronic nasal disease that is characterized by progressive atrophy of the mucosa and underlying bone of the conchae, with metaplasia of the pseudostratified columnar ciliated epithelium to a stratified squamous variety. The mucous membrane exudes a thick viscid secretion which dries rapidly and forms crusts which emit a characteristic foul odour. The condition is much more common in women than in men and usually begins about puberty, although it is also found in children. Its occurrence at puberty has suggested the possibility that some disturbance of the endocrine system is responsible for its development (Lautenschlager, 1923, 1924; Pratt, 1931; Ruskin, 1932, 1942; Brownlie-Smith, 1952) and this is supported by the findings of Mackenzie (1898), Fleiss (1897) and Klotz (1936) who showed that atrophic rhinitis became much worse during pregnancy and menstruation than at any other time.

Dorochenko (1937), Mortimer, Wright and Collip (1937) and Blaisdell (1938) evaluated the use of œstrogen in this condition by clinical trials. They found that the administration of œstrogenic hormones produced a marked improvement in most cases. This was the experience of Bernheimer and Soskin (1940) who showed that while œstrogen administration brought relief in some cases it did not invariably do so, and that those who obtained relief were also relieved by the topical application of prostigmin methyl sulphate to the nasal mucosa. This seemed to indicate that the vasodilator action of œstrogen on the nasal mucosa was the factor responsible for the symptomatic relief.

Ruskin (1942), finding that some patients were not improved, attempted to rationalize the treatment of atrophic rhinitis with œstrogenic hormones by recognizing two pathological types:

(1) atrophic rhinitis of unknown ætiology, and
(2) secondary atrophic rhinitis due to prolonged nasal infection.

He stated that primary atrophic rhinitis was characterized by endarteritis of the mucosal vessels, and that the atrophic process resulted from the

diminished blood supply to the mucosa. In these cases the vasodilator effect of œstrogenic hormones was of value. This finding agrees with that of Eagle, Baker and Hamblin (1939), Hall and Macleod (1942) and Saltzman (1944) who believed that œstrogen lack was the predominating factor in atrophic rhinitis. A constant finding in those under treatment was a marked increase in the absorptive capacity of the nasal mucosa. Saltzman paralleled his studies with those of Davies (1935) on senile vaginitis and stated that the histological changes were essentially the same in both disorders, while Eagle, Baker and Hamblin compared nasal biopsies before and after treatment but were unable to demonstrate that any changes had taken place.

Schaeffer (1932) believed that atrophic diseases were associated with premature senility. He based his opinion on the fact that the cavernous blood spaces of the nasal mucosa are at a maximum during active sexual life and decrease with the onset of sterility. These changes have been confirmed recently by Wustrow (1951).

Mortimer, Wright and Collip (1937) while agreeing that the administration of œstrogen is beneficial, showed that the majority of patients with atrophic rhinitis had a pituitary dystrophy. This was demonstrated by taking lateral X-rays of the head. The pituitary fossa was found to be enlarged in patients with atrophic rhinitis when compared with the X-rays of a control group of healthy adults. In view of this they considered that atrophic rhinitis was caused by a generalized disorder of the endocrine system. This was the view of Briani (1934), although he implicated functional deficiency of the parathyroid glands as the prime ætiological factor. Tilley (1919), Watson-Williams (1952) and Thomson and Negus (1955) have also stated that atrophic rhinitis is influenced by the endocrine system, but the mechanism underlying this effect remains obscure.

It is now known that some biological processes are controlled by hormone mechanisms (Krebs, 1956). As histochemical methods give some indication of the chemical composition of tissues, these techniques have been used in the present study of atrophic rhinitis.

Materials and Methods

Nasal mucosa was obtained from the nasal cavities of fourteen patients with atrophic rhinitis undergoing operation under general anæsthesia. Care was taken to ensure that the specimen was the full thickness of the nasal mucosa; for this reason and to minimize trauma a sharp knife rather than biopsy forceps was used to remove it.

Each specimen was divided into two, one part being fixed in ice cold acetone and the other in ice cold 80 per cent. alcohol, and embedded in paraffin wax. Four specimens were fixed by the method of freeze substitution since it gave a better histological picture with more accurate

localization of intracellular substances, but it was not used routinely as it was sometimes inconvenient to use this method during operating sessions.

Serial sections were cut; each section being 7μ in thickness.

Apart from routine staining with hæmatoxylin and eosin, the following stains were used:

1. Iron hæmatoxylin and picrofuchsin (van Gieson) and Masson's trichrome for the demonstration of collagen.
2. Gordon and Sweet's stain for reticulin.
3. Southgate's mucicarmine for mucin.
4. Alcian blue for acid mucopolysaccharides.
5. The Periodic acid-Schiff (PAS) method (Hotchkiss, 1948) for the demonstration of polysaccharides. In some instances the acid reducing rinse was not employed: this enhances the demonstration of collagenous tissue, as suggested by Lillie (1953). The PAS-positive material was differentiated according to the scheme outlined by Pearse (1960).
6. Toluidine blue (0·5 per cent. for 30 minutes) and azure A (0·01 per cent. for 5 minutes or 0·1 per cent. for 10 minutes) to demonstrate metachromasia.
7. Toluidine blue (0·5 per cent. for 30 minutes) and the methyl green pyronin method for ribonucleic acid (RNA). In the latter technique, pyronin Y was used as advocated by Kurnick (1955). Control sections were stained after treatment overnight with 10 per cent. perchloric acid at 4°C. (Seigel and Worley, 1951).
8. The Feulgen reaction to demonstrate deoxyribonucleic acid (DNA) (Pearse, 1960).
9. Non-specific estrase was demonstrated by the α-napthol acetate method (Pearse, 1960).
10. Cholinesterase was demonstrated by the myristoyl choline method (Pearse, 1960).
11. Alkaline phosphatase was demonstrated by the calcium-cobalt method of Gomori (1946), with the addition of magnesium ions to activate the enzyme as suggested by Kabat and Furth (1941). The substrate used was sodium β-glycerophosphate and the incubation period one hour.

Results

The atrophic mucosa in the present study is characterized by:

1. the presence of stratified squamous epithelium at sites where columnar ciliated epithelium is normally seen,
2. the dilatation of capillaries, and
3. a decrease in the number and size of the compound alveolar glands.

All stages in the metaplastic change from columnar ciliated to stratified squamous epithelium are found. The tall columnar cells lose their cilia and begin to flatten. Fewer goblet cells are seen (Fig. 1). The cytoplasm of the flattened cells is filled with fine granular material and the nuclei are round and centrally placed. These cells lie on one another giving a stratified appearance (Fig. 2). In the final stage of squamous stratification

All the photomicrographs are of atrophic rhinitis except Fig. 4b which is taken from normal nasal respiratory mucosa.

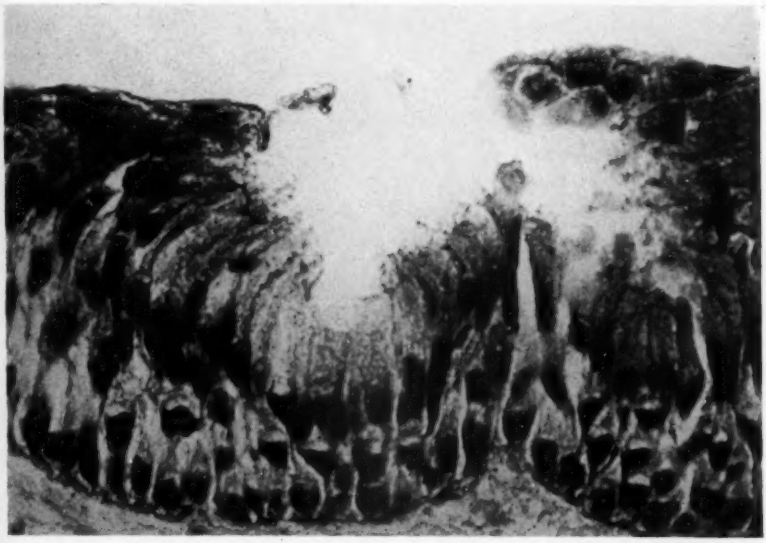

FIG. 1.
Stages in the metaplastic change from columnar ciliated to stratified squamous epithelium. H. and E. × 540.

four layers of cells can be identified. Many mitotic figures are seen in the deepest layers (Fig. 6). These cells and those of the adjacent superficial layer are larger and oval in outline with a round nucleus, centrally placed. The cytoplasm of these cells is filled with fine granular material and they appear to be connected by intracytoplasmic threads having the typical appearance of tonofibrils that are thought to be the precursors of keratin (Fig. 3). The nuclei of these cells begin to fragment in the next layer and the cell outlines become indistinct and flattened. Finally a mass of keratin is seen lying on the surface of the stratified squamous epithelium (Fig. 6).

The basement membrane when present is very thin.

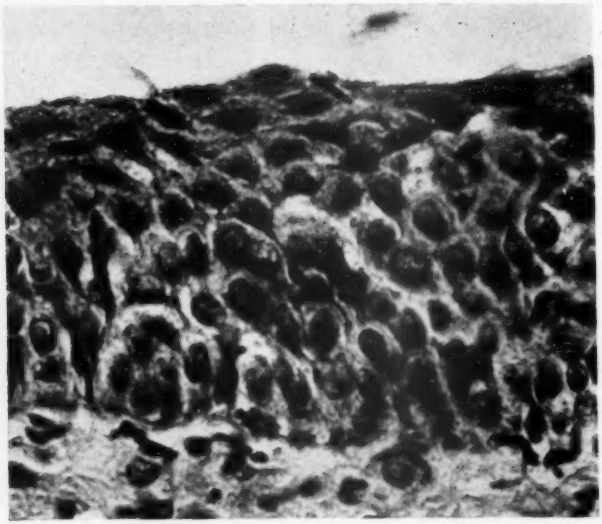

FIG. 2.
Atrophic rhinitis. Stratified squamous epithelium. H. and E. × 540.

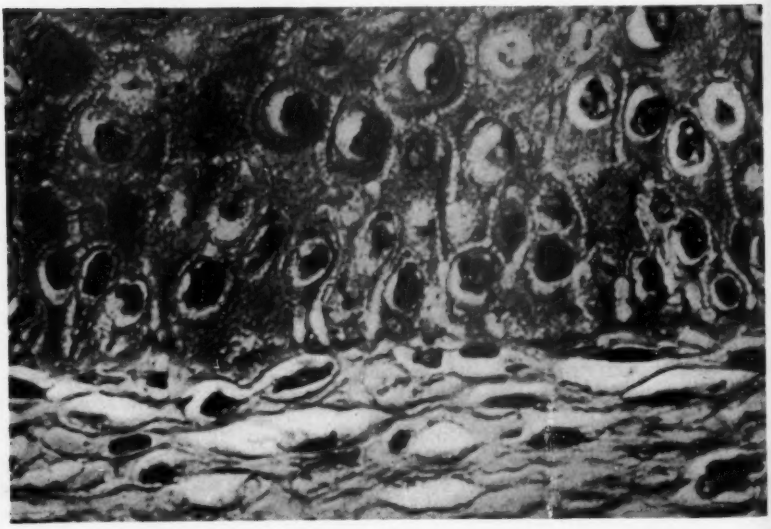

FIG. 3.
Tonofibrils between the cells in the deeper layers of the keratinizing stratified squamous epithelium. H. and E. × 540.

Typical serous and mucous glands are seen (Fig. 5) but they are reduced in size and number. In the subepithelial layers there is an increase in the amount of fibrous tissue, while inflammatory cells are present lying mainly immediately below the epithelium.

The arterioles appear to be normal but the capillaries are markedly dilated and are lined by large endothelial cells, the cytoplasm of which contains fine granular material, and their nuclei are large and oval and centrally placed (Fig. 4*a*, 4*b*).

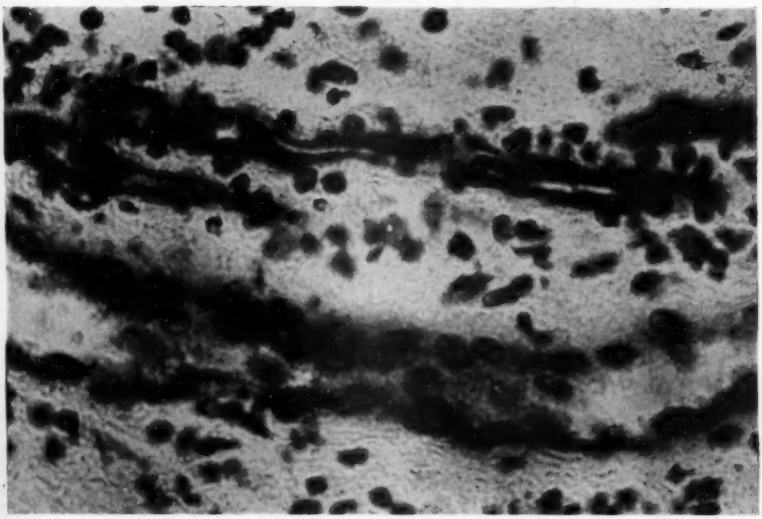

FIG. 4*a*.
Dilated capillaries lined by large endothelial cells. Gomori's alkaline phosphatase method. × 540.

Histochemistry

As the epithelium loses its cilia and the columnar cells flatten, PAS-positive granules are seen in the cytoplasm of some of the more superficial cells. The cytoplasm of the cells of the deepest layers of stratified squamous epithelium is PAS-negative. As the cells are pushed towards the surface by this actively dividing layer PAS-positive granules are seen in their cytoplasm. This reaction becomes pronounced as the cells become more superficial, until a dense PAS-positive coagulum is seen in the keratinizing layer (Fig. 7). The increase in density of PAS-positive material is paralleled with an increase of staining reaction for ribonucleic acid (Fig. 8).

The basement membrane when present has a PAS-positive reaction (Fig. 9) and contains a well marked layer of reticulin (Fig. 10).

The presence of a mucicarmine an Alcian blue positive reaction corresponds to the distribution of PAS-positive material.

Analysis of the PAS-positive material shows that it contains a carbohydrate-protein complex and acid mucopolysaccharide like the epithelium and glands of the normal nasal respiratory mucosa.

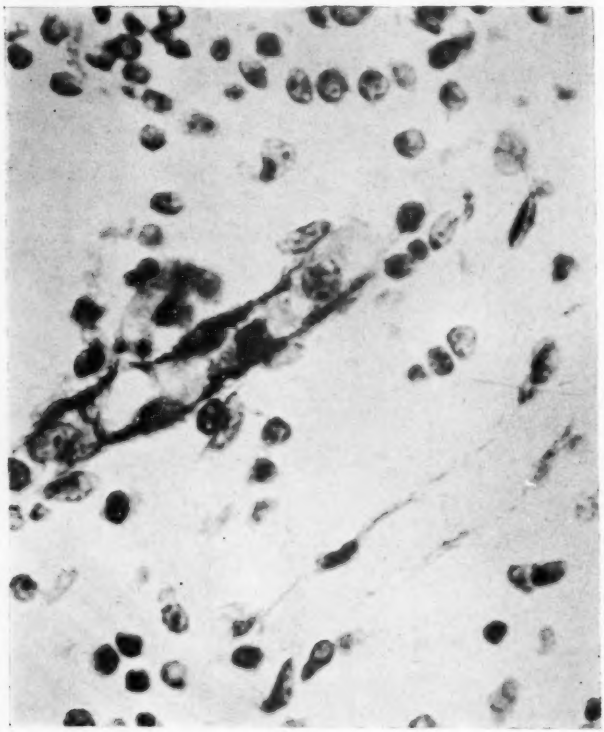

FIG. 4*b*.

Capillaries in normal nasal mucosa. Gomori's alkaline phosphatase method. × 540.

The cytoplasm of the large endothelial cells lining the dilated capillaries has a positive reaction for alkaline phosphatase (Fig. 4) and non-specific esterase.

There is no change in the distribution of deoxyribonucleic acid and ribonucleic acid, with the exception of the stratified squamous epithelium already mentioned.

There is no reaction for acetyl-cholinesterase.

Discussion

Atrophic rhinitis was formerly a very common condition. It is now relatively rare. The incidence of chronic nasal infection has decreased also and it is possible that many cases of atrophic rhinitis were secondary to chronic nasal infection. Schönemann (1902), Lautenschlager (1923, 1924) and Eggston and Wolff (1947) considered that all cases of atrophic rhinitis were due to chronic infection. This induced endaritis and periarteritis of the terminal arterioles of the nasal mucosa, which resulted in a diminished blood supply to the nasal mucosa and produced the atrophic changes of atrophic rhinitis.

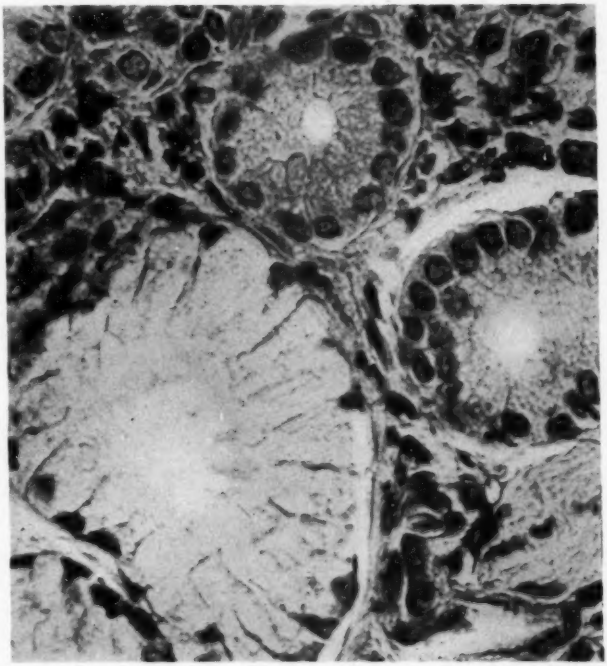

FIG. 5.
Mucous and serous glands. H. and E. × 540.

Successive workers on atrophic rhinitis confirmed the histopathological findings of their predecessors. These were:

1. decrease in thickness of the mucosa;
2. loss of cilia from the columnar ciliated epithelium;

3. metaplastic change of the columnar ciliated epithelium;
4. degeneration and atrophy of the goblet cells and serous and mucous glands;
5. increase in the thickness of the basement membrane which contains more collagen;
6. diffuse fibrosis in the mucosa; and

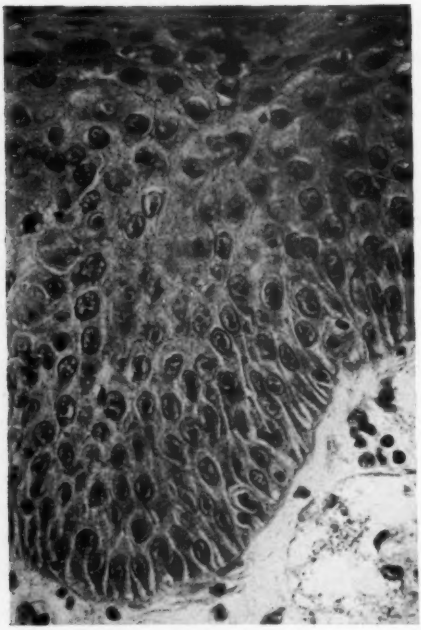

FIG. 6.
Stratified squamous keratinizing epithelium. H. and E. × 540.

7. infiltration of lymphocytes, plasma cells and polymorphonuclear-leucocytes mainly around the blood vessels.

Although the changes in the epithelium and glands have been confirmed, other histological features of atrophic rhinitis in the present study differ from this picture in that:

1. the basement membrane is not thickened;
2. infiltration with inflammatory cells and fibrosis are not marked features; and
3. there is no endarteritis or periarteritis of the terminal arterioles.

The characteristic feature of atrophic rhinitis in the present study is a dilatation of the capillaries.

As Shambaugh (1931) and Hollender (1944) have shown, thickening of the basement membrane, infiltration with inflammatory cells, fibrosis and endarteritis or periarteritis of the terminal arterioles are characteristics of chronic infection of the nasal mucosa and, as they are absent

FIG. 7.

Increase in the PAS-positive reaction in the more superficial cells of the stratified squamous epithelium. PAS counterstained with hæmatoxylin. × 540.

from the atrophic mucosa under study, either the nature of atrophic rhinitis has changed or there are two distinct pathological processes each giving rise to a similar clinical picture.

Ruskin (1942) realized that there were two kinds of atrophic rhinitis which he designated primary and secondary. Ruskin's primary atrophic rhinitis was characterized by endarteritis of the terminal arterioles without

infection, ulceration of the mucosa and sclerosis of the lateral wall of the nose. His secondary atrophic rhinitis, on the other hand, was characterized by a round cell inflammatory reaction involving the "distensile mechanism" of the mucosa. Atrophy of the bone of the lateral wall of the nose was a feature of this condition. Although the lateral nasal bony wall was thicker and more dense in primary atrophic rhinitis, the nasal cavities,

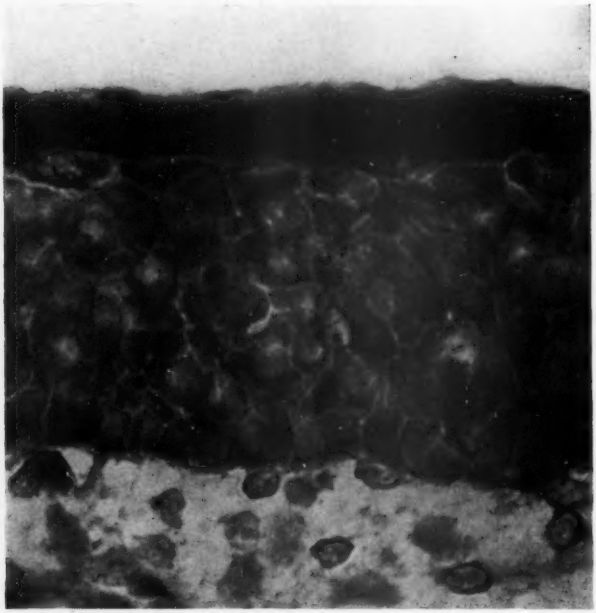

FIG. 8.
Increase of RNA in the more superficial cells of the stratified squamous epithelium. Methyl green pyronin technique. × 540.

as in secondary atrophic rhinitis were much wider, and clinically the conditions were identical. Lautenschlager (1924) observed that some cases of atrophic rhinitis had a very thick and dense lateral nasal bony wall. He considered this an unusual finding in view of the marked atrophy of the turbinate bones. Another distinguishing feature was that primary atrophic rhinitis improved after the administration of œstrogenic hormone while secondary atrophic rhinitis did not. This stimulated Ruskin to investigate the relationship of œstrogens to atrophic rhinitis. He was able to extract a gonadatrophic hormone from the nasal mucosa of beef cattle and, unlike Eggston (1940) believed that it came from the pharyngeal

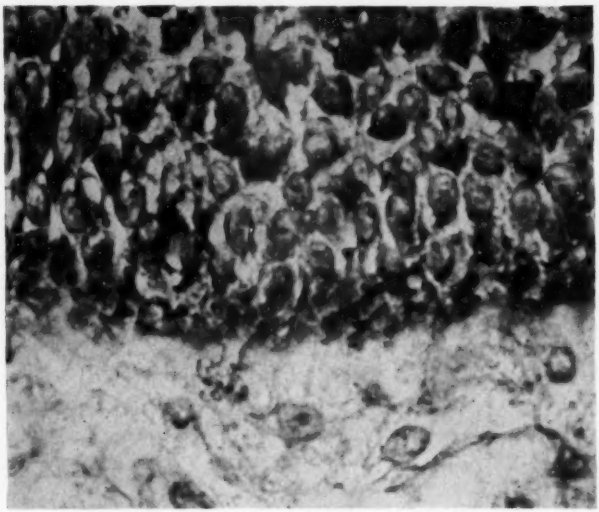

FIG 9.
PAS-positive reaction of the basement membrane of the stratified squamous epithelium. PAS counterstained with hæmatoxylin. × 540.

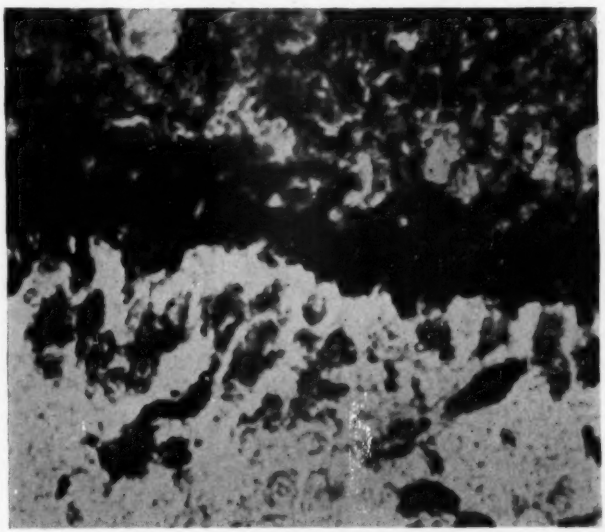

FIG. 10.
Reticulin in the PAS-positive basement membrane. Gordon and Sweet's method. × 540.

pituitary gland. On this evidence he stated that:- "since the pituitary gland is concerned with blood vessel tone, the pronounced thickening of the blood vessel walls shown in the pathological picture of atrophic rhinitis is the end result of tonic overaction of the vasomotor fibres, caused perhaps by a deficiency of the pharyngeal pituitary gland." It is difficult to understand precisely what Ruskin meant by this statement. If he meant that pitressin, the posterior lobe hormone, produced these changes, then a generalized endarteritis and a raised blood pressure would be expected in atrophic rhinitis, but this does not occur. Furthermore, the pharyngeal pituitary gland is developed from the cell mass that forms the anterior lobe of the pituitary gland and so could not secrete posterior lobe hormone (Ham, 1957; Eggston and Wolff, 1947).

Ruskin's view of the ætiology of atrophic rhinitis appears to be untenable.

It seems probable that infection is the cause of the endarteritis that may be seen in this disease and that with the means available to control infection the incidence of this type of atrophic rhinitis has decreased. This is supported by the present study in which no endarteritis was seen in the blood vessels of the nasal mucosa. The characteristic change was a dilatation of the capillaries. The presence of these dilated capillaries had been observed previously by Frankael (1879, 1882), Schönemann (1902) and Lautenschlager (1924), but they did not comment on their significance, possibly because they were unable to correlate them with their concept of the ætiology of atrophic rhinitis. The endothelial cells lining these capillaries have more cytoplasm than those lining the capillaries of the normal nasal mucosa and show a more strongly positive reaction for alkaline phosphatase. High concentrations of alkaline phosphatase are associated with the absorption and laying down of bone (Bourne, 1956), and absorption of the bone of the lateral nasal wall is a feature of atrophic rhinitis. Young (1957) has shown that bone chips introduced beneath the nasal mucosa in this condition (to reduce the nasal airway) are rapidly absorbed. This seems to indicate that there is some local condition inducing rapid bone absorption, and this may be associated with the increase in alkaline phosphatase in the cytoplasm of the endothelial cells.

Because of the atrophy of the lateral nasal bony wall, Briani (1934) considered that parathyroid disease was an ætiological factor in this condition, but as no other bony defects are seen in atrophic rhinitis, and the condition is not associated with hyperparathyroidism, Briani's postulation appears to be unreasonable.

It has been shown that after the injection or implantation of œstradiol in the rabbit and rat, and during pregnancy in the rabbit, there is a dilatation of the blood vessels in the nasal mucosa (Taylor, 1959). Capillary dilatation is a feature of the atrophic rhinitis that is not secondary to infection and the question arises whether high œstrogen levels are an ætiological factor in this disease.

Atrophic rhinitis is much commoner in women, while Fleiss (1897), Mackenzie (1898) and Klotz (1936) observed that some cases are much worse during pregnancy and menstruation than at any other time. Harrison (1957) showed that prolonged administration of œstrogenic hormones in man changes the columnar ciliated epithelium into stratified squamous epithelium. This seems to indicate that high œstrogen levels are an ætiological factor in atrophic rhinitis, but high œstrogen levels can produce vasomotor symptoms (Taylor, 1959), and there is no evidence that this type of vasomotor rhinitis leads to atrophic rhinitis. Harrison's work must be accepted with further reserve since several of his biopsies were taken from respiratory mucosa that had been cauterized repeatedly. The metaplastic change, therefore, could be due to trauma and not to the prolonged administration of œstrogen.

Hilding (1932), Schaeffer (1932), Hollender (1944) and Messerklinger (1954) believe that trauma, the drying effect of inspired air and a reduction in blood supply to the nasal mucosa are the principal factors underlying the metaplastic change in the epithelium in atrophic rhinitis. Ruskin (1932) and Eggston and Wolff (1947) are more specific; they consider that the reduction of nutriment and oxygen supply, and the accumulation of waste products occasioned by the distance the keratinizing cells are from the capillaries, determine the process. That true keratinization is occurring is borne out by the appearance of tonofibrils in the deeper layers. They represent the first sign of the material that becomes so abundant as the cells grow older (Leuchtenberger and Lund, 1951). Ham (1957) considers that all keratinizing squamous epithelia have some measure of self determination and that loss of blood supply is not the determining factor, on the grounds that epidermis transplanted into subcutaneous tissue, and malignant epidermal tumours that invade underlying connective tissue, continue to form keratin even though they have an adequate blood supply.

It is interesting to note that under conditions of prolonged vitamin A deficiency certain other kinds of specialized epithelia in the body become keratinized, but there is no evidence to suggest that this is a factor in atrophic rhinitis.

The Surgical Treatment of Atrophic Rhinitis

Many attempts have been made to treat atrophic rhinitis surgically (Clerici and Manzini, 1955). All these methods depend on reducing the nasal airway, and are based on the assumption that the drying effect of inspired air is a major factor in the causation or progression of the disease. Although several authors claim to have been successful (Clerici and Manzini, 1955; Rethi, 1959), their long term results have not been published. In the present study six methods of reducing the nasal airway have been used; five involve the introduction of various substances

beneath the mucosa of the floor of the nose and septum, and the sixth method reducing the size of the anterior nasal apertures. The advantages and disadvantages of each method may be conveniently listed.

1. *Bone chips or strips* removed from the ileum have the disadvantage that they are difficult to insert and are absorbed rapidly (*vide* supra).
2. *Split polythene tubing* is easy to insert but tends to extrude easily.
3. *Plastic sponge* is easy to insert, but tends to extrude in a high proportion of cases and when this occurs the pieces are difficult to remove.
4. *Solid dental plastic* is easy to insert and remove and is fairly effective in reducing the nasal airway.
5. *Plastic gauze* (corlene mesh) is easy to insert and remove but tends to extrude.
6. *Partial closure of the anterior nares* (the only possible method in children), has the disadvantage that the nasal cavities cannot be inspected adequately.

There was no evidence that the disease process had been arrested, but in those who had an adequately reduced nasal airway there was symptomatic relief.

Summary

In the present study 14 cases of atrophic rhinitis collected over a period of 3 years have been investigated by histological and histochemical methods.

The nasal respiratory mucosa in atrophic rhinitis undergoes a metaplastic change from tall columnar pseudo-stratified ciliated epithelium to a keratinized stratified variety. The compound tubulo-alveolar glands are reduced in size and number and the subepithelial capillaries are dilated. The cytoplasm of the cells of the dilated capillaries has a positive reaction for alkaline phosphatase and non-specific esterase.

Atrophic rhinitis was formerly a common condition and is now relatively rare. The incidence of chronic nasal infection has decreased also and it seems probable that in the past most atrophic rhinitis was due to an inflammatory process producing endarteritis and periarteritis of the terminal arterioles. This resulted in a diminished blood supply producing the atrophic changes of atrophic rhinitis: the vasodilator effect of œstrogens would therefore be of value in this condition.

The characteristic feature of the atrophic mucosa in the present study is a dilatation of the capillaries; inflammatory changes are not marked. The cytoplasm of the component cells of the dilated capillaries contains alkaline phosphatase. In certain sites this enzyme is associated with the absorption and laying down of bone and as absorption of the lateral nasal bony wall is a feature of atrophic rhinitis, this may be associated with the increase in alkaline phosphatase in the cytoplasm of the endothelial cells of the dilated capillaries.

Two types of atrophic rhinitis may therefore be postulated:

Type I: characterized by endarteritis and periarteritis of the terminal arterioles—the result of chronic infection; and

Type II: characterized by the dilatation of capillaries.

There is some evidence to indicate that Type II atrophic rhinitis is made worse by the administration of œstrogens which may play some part in the ætiology of the condition.

Several surgical methods of treating atrophic rhinitis are described, all for the purpose of reducing the nasal airway. The advantages and disadvantages of each are mentioned.

The effect of the operation is palliative. In no case is it curative.

Acknowledgements

We wish to express our thanks to Professor F. Davies for his advice and encouragement during the carrying out of the research reported here, and for the facilities he has made available in his Department in the University of Sheffield. We are most grateful to Dr. R. M. H. McMinn for his advice and criticism, and to Mr. J. H. Kugler for his technical advice and Mr. J. H. Morrill for the photomicrographs.

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CLINICAL RECORDS

A CASE OF ETHMOIDAL OSSIFYING FIBROMA OBSERVED IN A CHILD SEVEN YEARS OLD

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MANY cases of ossifying fibroma are to be found in the otolaryngic literature of the last 50 years. This is a particular kind of tumour, often observed at the level of the facial and cranial bones. The ossifying fibroma is a benign tumour with slow development; according to their histological characters it has been sometimes referred to as *"psammo-osteoid-fibroma"* (Gögl), *"tumeur fibro-ostéoïde à calcification atypique"* (Benjamins), *"osteoidoma"* (Beck), *"fibrous osteoma"* (Phemister and Grimson), *"psammoma"* (Fry and Delong), *"osteoid fibroma"* (Smelt), *"osteofibroma"* (Agazzi and Belloni). Phemister and Grimson call *"fibrous osteomas"* the cases where mature bone tissue with extensive ossification can be observed, and *"osteofibroma or ossifying fibromas"* the cases where the fibrous tissue with immature bone predominate.

The ossifying fibroma has intimate relationship with another type of tumour to be observed at the level of the maxillary bones: the cementoma. The ossifying fibroma and the cementoma may be considered as having a common origin : in the case of ossifying fibroma the bone-forming process gives rise to bone or osteoid tissue, in the case of cementoma it gives rise to the cement (Agazzi e Belloni).

The relationship between ossifying fibroma and monostotic fibrous dysplasia is very significant (Skolnik and Fornatto). Monostotic fibrous dysplasia is to be found in the femur, tibia, maxilla and mandible of older children and young adults. Sometimes we observe also an abnormal pigmentation of the skin, a premature sexual development and signs of hyperthyroidism. Many AA. (Lichtenstein; Mallory; Schlumberger; Finzi; Agazzi and Belloni; Szanto) state that the ossifying fibroma is a particular kind ot the monostotic fibrous dysplasia. Smith and Zavaleta consider ossifying fibroma as synonymous with monostotic fibrous dysplasia of cranial or facial bones.

Geschickter and Copeland, Smith and Zavaleta think that ossifying fibroma can evolve into osteoma. Smith and Zavaleta distinguish three types of ossifying fibroma: young, intermediate and mature form: the ossifying fibroma progresses from the young form to the intermediate and the mature ones and there is a parallel between the age of the patient and the maturity of the tumour. These AA. observed also an evolution of the mature form of ossifying fibroma to a transitory osteoma and then to the mature form of the osteoma.

The cases of ossifying tumour of the ethmoid are observed very seldom.

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Perusal of the literature brought to light a total of eleven cases, described by Scalori; McKibben and Casey; Scholtz; Wild and Heimendinger; Secretan; Benjamins; v. Eicken and Schürmann; Woodruff; Dintenfass *et al.*; Balzer; Brunner.

The purpose of this paper is to report a case of ethmoidal ossifying fibroma we observed in a child aged seven years.

FIG. 1.

Report of the Case

C. Filippo—A boy aged seven years, born in Vittoria (Ragusa). The patient was admitted to the ENT Department of the Turin University on *April 18th, 1959*. For about two years the child's parents noticed a progressive displacement of the left eyeball to an external position. For about one year the patient suffered from epistaxis with left nasal stenosis. On admission the nasal septum was deviated to the right; the left middle meatus was found to be occupied by a firm granular red mass; the left eye-ball was displaced to an inferior, lateral and anterior position. There was a slight exophthalmos. The left nasal bone was enlarged, causing the inner canthus of the left eye to be displaced laterally from a symmetrical position. Movements of the eye were normal, as was the fundus oculi. Blood chemistry and urinalysis were normal.

The X-ray examinations showed a homogenous rounded mass in the superior half of the nasal cavity and occupying the ethmoidal labyrinth and the medial portion of the orbit (Fig. 1). The mass was enveloped by a more dense zone (Fig. 2).

The patient was operated on *May 12th, 1950* (Prof. F. Brunetti). The operation was executed in general anæsthesia. A para-nasal incision in the left side, encircled the vestibulum nasi. The pyriform margin and the ascending process of the superior maxilla were removed so as to encircle a big mass with osteofibrous capsule, occupying the ethmoid, the nasal cavity, the orbit and the sphenoid sinus. The mass was removed as a whole, since it is not adherent to the

FIG. 2.

nasal septum, to the nasal cavity or to the orbit. There was only a peduncle at the level of the cribriform plate.

The excised mass was the size of a small hen's egg, and is enveloped with an osteofibrous capsule, as thick as an egg shell.

The microscopic examination showed a dense fibrous stroma composed of interlacing bands of fusiform cells, with acidophilic cytoplasm, showing a tendency towards whorl formations. The nuclei were fairly uniform in size and shape and in staining qualities. There were sharply circumscribed, concentrically laminated basophilic bodies (Fig. 3), and numerous calcified and non-calcified bony trabeculae (Fig. 4), containing relatively few osteocytes and osteoid trabeculae (Fig. 5). There were also numerous islands of bone surrounded by osteroid tissue with prominent peripheral osteoblast layers. The bony trabeculae compose a discontinuous envelopment covering the tumour (Fig. 6).

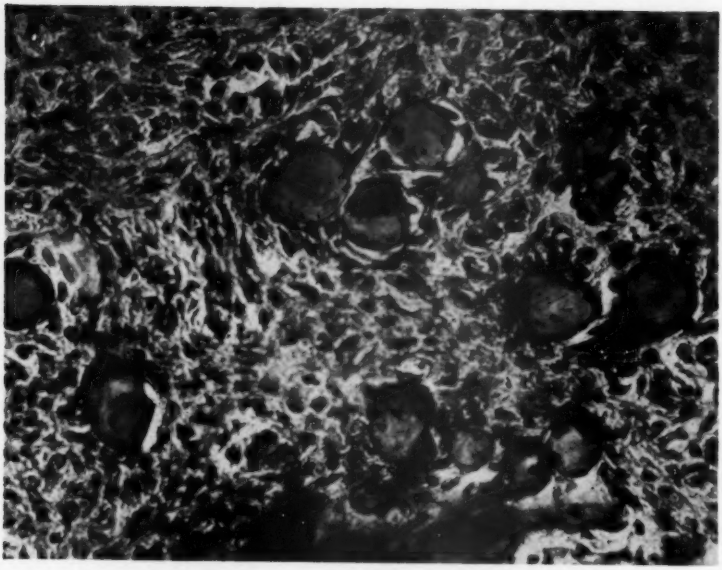

FIG. 3.

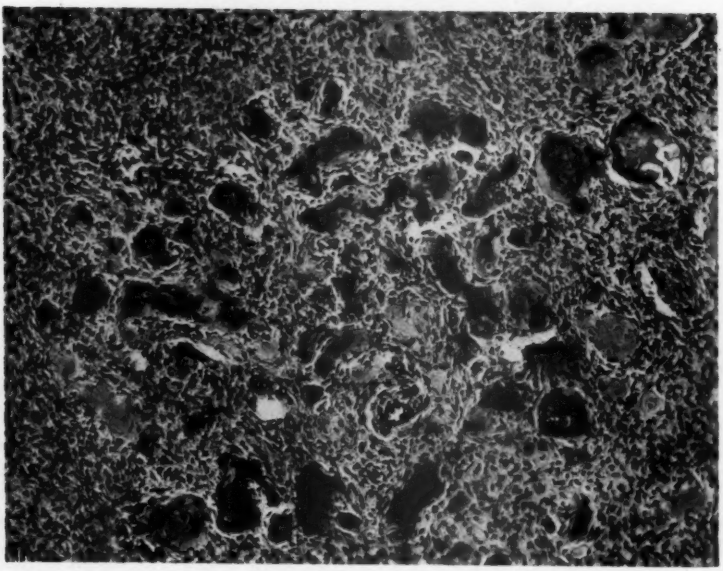

FIG. 4.

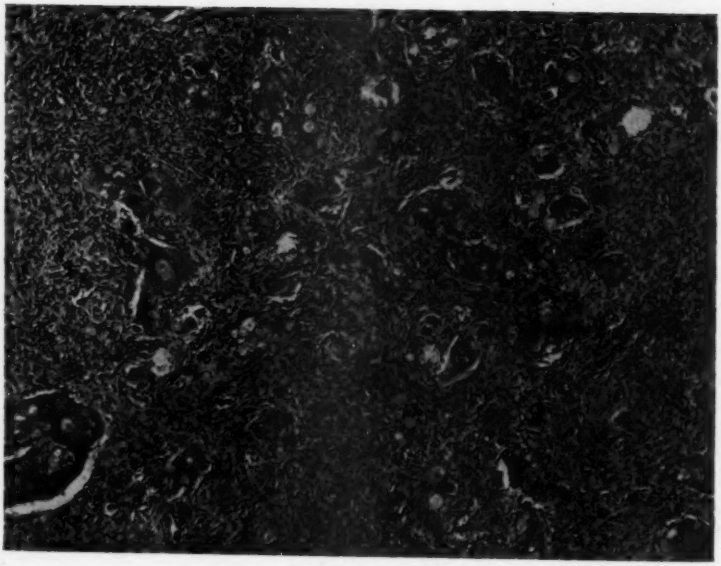

FIG. 5.

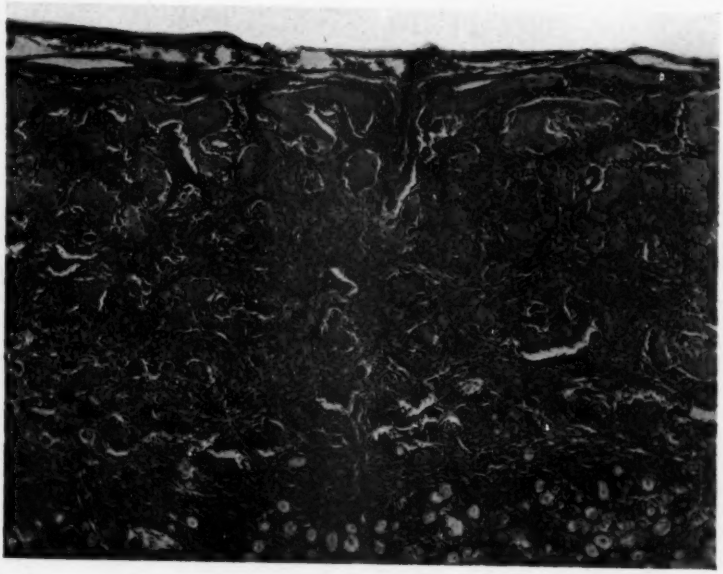

FIG. 6.

Histological diagnosis: ossifying fibroma (Prof. G. Mottura).

On *May 27th, 1959*, the patient left the clinic. No recurrences were present a year after the surgical removal.

Conclusions and Summary

A case of ethmoidal ossifying fibroma in a child of seven years is described. The exact site of origin is emphasized. Almost all recorded cases of ossifying fibroma have originated at the level of the superior maxilla, the inferior maxilla or the frontal bone. Examples of ethmoidal origin are, on the contrary very scarce and only eleven such cases could be found in the literature. For this reason it was thought worth while to publish the present case.

Most of the recorded cases of ossifying fibroma occurred in patients of less than twenty years of age, and it is seldom found in older subjects. The age of the present case is in agreement with the published experience.

An important histological feature was the presence of a capsule composed of lamellae of mature bone tissue, enveloping the tumour like a shell. By contrast the interior was composed of an abundant connective tissue stroma in which were embedded trabeculae of osteoid tissue and sharply circumscribed, concentrically laminated basophilic bodies. The osteoid tissue was much more abundant than the mature bone tissue, suggesting that the tumour belonged to the intermediate group according to the classification of Smith and Zavaleta. Its extensive, though not invasive growth, the uniformity of the nuclei and the absence of mitotic figures indicate its benign nature. Varying histological appearances in different parts of the tumour, the presence of osteoid and bone tissue with prominent peripheral osteoblast layers are expressions of the continuous transformations which this tumour undergoes during its growth.

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CANCRUM OF EAR—A RARE CASE

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CANCRUM oris is a well-known complication of measles and other acute infectious fevers, but cancrum of the ear is a rare complication and no mention of such a condition occurring during or after measles has yet been reported in literature, though acute otitis media and mastoiditis are frequent complications of an attack of measles.

The case history is as follows:

A three year old male child was brought to E.N.T. Department of the King Edward VII Memorial Hospital, Bombay, on *February 4th, 1960*, in a state of marked emaciation and toxæmia with a large ulcer surrounding the left auricle.

O.D.P.: The child had an attack of measles in the middle of *January 1960* which had lasted for a week; during this attack a watery discharge from the left ear was seen for which no treatment was given. Ten days after the onset of otorrhœa a black patch appeared on the skin in the post-auricular groove on the left side which spread very rapidly becoming an ulcer in four days and extending to surround the left auricle on all sides. The skin of the left auricle, thus devoid of nutrition during this period, became dry, leathery and charcoal black in colour.

Past History: No history of trauma, exposure to excess of temperature, no history of application of any drugs or history of any other illness previous to measles.

Local Examination: A large ulcer circular in shape, 3-inches diameter, with the auricle in centre in state of dry gangrene.

Margins of ulcer were well defined.

Floor: In the centre was the auricle—the rest of the ulcer was covered with foul smelling purulent discharge, slough and unhealthy granulation tissue.

On gently pulling the auricle forwards to examine the post-auricular groove the whole auricle together with a part of cartilaginous external canal and a part of the surrounding slough came off loose from the rest of the body revealing a deep gap in the centre of the ulcer. There was no bleeding. The structures exposed were as follows:

(1) Posteriorly the whole mastoid bone up to the tip, the cortex being normal.

(2) Anteriorly the whole left ramus of the mandible below up to the angle and above up to the temporomandibular joint.

(3) The left temporomandibular joint was exposed with destruction of its capsule, showing the joint line.

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(4) Behind the ramus a destruction of the structures of pterygoid fossa was noted, exposing the pharyngeal mucous membrane, without a pharyngeal fistula.

(5) Mass of granulation tissue in region of middle ear.

(6) Complete destruction of left parotid gland.

(7) Complete destruction of extramastoid part of left facial nerve leading to left infranuclear facial paralysis.

(8) Complete thrombosis and obliteration of jugular bulb and upper part of internal jugular vein.

(9) Pulsation of internal carotid artery could be seen deep in the floor of the ulcer.

Lymph glands draining the area—upper deep cervical lymph nodes were palpable on left side which were firm, discrete and small.

General Examination: Extremely dehydrated, emaciated and moribund, unable to sit up unaided or even move the limbs. Cry very feeble. Left infranuclear facial palsy and exposure keratitis with corneal ulcer left eye. Temperature 102° F. Pulse 160 per minute, thready, respirations 34 per minute, weight 9½ lbs.

Mucus membrane of mouth and conjunctiva: dry, shrivelled up and pale. Anæmia marked.

No rash of any kind on the skin.

The patient was immediately admitted, investigated and treated on following lines:

Investigations

(1) Culture and antibiotic sensitivity of organisms obtained from the discharge from the ulcer—*B. proteus*—sensitive to chloromycetin, streptomycin and neomycin. Resistant to sulpha, penicillin and tetra- and oxytetracylin.

(2) Throat swab culture: staphylococcus and pyocyaneus coagulase positive.

(3) X-ray chest: Atelectasis right lower lobe with small area of pneumonitis right base. This patch disappeared as was seen in a repeat X-ray chest after eight days of treatment.

(4) Urine: Highly concentrated, absence of albumin and sugar. Microscopic—oxalate crystals.

(5) Biopsy of the margin of the ulcer showed changes compatible with clinical diagnosis of cancrum.

(6) X-ray mastoids showed sclerotic mastoid on both sides.

Treatment

Two blood transfusions 250 c.c. each were given at an interval of four days.

Intragastric feeding, milk, one egg per day, cod liver oil, protein hydrolysate.

Multivitamins by injection daily.

Six-hourly dressing of the ulcer by Eusol packs.

Inj. Streptomycin ½ gm. twice a day for five days, then ¼ gm. twice a day for 30 days.

Cauterization of margins of the ulcer with 20 per cent. silver nitrate.

General nursing care.

FIG. 1.
Showing ulcer after aurical came off.

FIG. 2.
Showing complete healing, with external auditory canal in centre.

The child responded very well to the above treatment. The temperature gradually came down to normal in six days. The child started taking oral feeds by 8th day. The ulcer started healing by epithelization from the margin with a complete healing in one and a half months. The epithelium also grew into the ear canal leaving a dry hole in the centre of the ulcer.

The child was discharged after two months when his weight was 16 lbs. The child was quite active and was able to stand up unaided.

The last follow up on *20.2.1961* showed completely epithelized scar with a dry hole in region of the ear canal.

There was no trismus.

Infranuclear facial paralysis left side.

Healed corneal ulcer left side with opacity.

Child very active, walking freely. Weight 19 lbs.

This case is interesting due to its rarity and the remarkable healing which occurred with only conservative line of treatment and proper nutrition.

Acknowledgement

We thank Dr. Joe V. DeSa, M.S., D.L.O. (Lond.), the head of E.N.T. Department, K.E.M. Hospital, Bombay, for guidance and Dr. S. V. Joglekar, M.S., F.C.P.S., Dean, K.E.M. Hospital, Bombay, for allowing us to publish the case.

K.E.M. Hospital,
Bombay 12, India

OVAL WINDOW SURGERY IN THE TREATMENT OF MÉNIÈRE'S DISEASE—PRELIMINARY COMMUNICATION

By P. E. MOORE and BRUCE CORNISH (Auckland, N.Z.)

EIGHT cases of Ménière's disease are described for which labyrinthectomy had been advised. The method used was the transmeatal approach as for stapes surgery, with removal of the stapes to expose the vestibule. The vestibule was then suctioned and the utricular remnants curetted before reconstruction of the ossicular chain by replacing the stapes over vein graft by the Portmann method, or using the polythene and vein graft technique of Shea.

In certain cases a surprising degree of residual hearing has remained in spite of the fact that the vertigo was arrested. It is realized that consideration must be given to the possibility that these could be the spontaneous remissions of vertigo characteristic of the disease and the patients have been warned to this effect. But so far the freedom from vertigo for periods up to eight months is encouraging.

The operation would appear to be worth considering, since it is a minor procedure, can still be followed by total destructive labyrinthectomy if necessary and does apparently offer the patient a chance of retaining hearing which may continue at a useful level.

13 Symonds Street,
Auckland, C.I.,
N.Z.

LETTER TO EDITOR

To the Editor, *Journal of Laryngology and Otology.*

The Elms,
Market Rasen.

5th May, 1961.

DEAR SIR,—It must be a little unusual for two articles to appear in your journal describing carefully controlled work on one subject, but coming to quite different conclusions.

Ardran and Kemp state, "the cause of the pharyngeal diverticulum is clearly due to deranged function of the pharyngeal constrictors: the cricopharyngeus closes partly or completely from the pharyx and the contraction of the pharyngeal musculature upon the body of the bolus causes the protrusion to appear".

Kodicek and Creamer state, "the resting tone of the cricopharyngeus sphincter appears normal and on swallowing normal relaxation is recorded. No evidence has been found to support a theory of faulty relaxation of the cricopharyngeal sphincter as a cause of pharyngeal pouch".

As the latter authors state, it is difficult to explain the improvement of symptoms obtained by dilatation or division of the portion of the upper œsophagus containing cricopharyngeal muscle by their findings. Certainly it is not unusual to find considerable hypertrophy or fibrosis of the cricopharyngeus muscle during operations for pharyngeal diverticula.

Yours sincerely,

M. SPENCER HARRISON.

GENERAL NOTES

VIIème CONGRÈS INTERNATIONAL O.R.L.

Le VIIème Congrès International O.R.L. se tiendra du 23 au 29 juillet 1961 à Paris, à la Nouvelle Faculté de Médecine, Rue des Saints-Pères, sous la présidence de M. le Professeur Aubry.

Trois très importants rapports seront discutés:

1°) Les acquisitions récentes en pathologie et en thérapeutique de l'otosclérose.
Rapporteurs: MM. les Professeurs Sourdille, Sercer and Krmpotic, Weber, Ardouin, Larroude, Ferreri and Schambaugh.

2°) Indications et résultats après 5 ans, de la chirurgie et des associations radio-chirurgicales dans le traitement des cancers du larynx et de l'hypopharynx.
Rapporteurs: MM. les Professeurs Pietrantoni and Agazzi, Alonso, Casadesus, Chevalier-Jackson, Leicher, Leroux-Robert, Ormerod.

3°) Rapports entre l'allergie et les infections du nez et des bronches.
Rapporteurs: MM. les Professeurs Van Dishoeck, Clerici, Hlavacek, Voohorst, Mayer, Laskiewicz, Teracol.

De nombreuses réunions et festivités sont envisagées pour les Congressistes et leurs épouses. A la suite du Congrès, des excursions auront lieu; elles seront proposées dans un avant-programme et réalisées par les soins des Wagon Lits Cook, 22 rue de l'Arcade, Paris, qui sont notre agent officiel habilité pour les transports et réservations d' hôtels.

Pour tous renseignements, écrire au Dr. Henry Guillon, Secrétaire Général, 6 avenue Mac-Mahon, Paris.

TEMPLE UNIVERSITY SCHOOL OF MEDICINE

Philadelphia 40. Pa.

A "Short course in Audiology" is offered several times each year by the Section of Audiology, Department of Otorhinology, Temple University School of Medicine, Philadelphia 40, Pa.

The course will be one week in length and will encompass theoretical and clinical aspects of audition. Hearing testing and interpretation will be stressed. Office procedures, equipment and Industrial Audiometry will be discussed.

Further information may be obtained by writing to Philip E. Rosenberg, Ph.D., Director, Section of Audiology, Temple University Medical Center, 3401 North Broad St., Philadelphia, Pa.

General Notes

INTERNATIONAL SYMPOSIUM ON AUDIOSURGERY

The National School of Medicine and Work, the National Institute of Medicine, and the Centre of Surgical Specialities have organized an International Symposium on Audiosurgery in Madrid in August 1961, on 2nd, 3rd and 4th. The Chairman will be, Dr. Francisco Antoli-Candela.

The subjects to be considered and discussed will be the Audiosurgery of the congenital defects of the ear, the chronic suppurative processes of the ear and its sequelae, and otosclerosis. The surgery of the facial nerve will also be considered. There will be surgical sessions and simultaneous translations.

An official lunch has been arranged and will be included in the subscription to the Symposium. On August 5th there will be a visit to the "Escorial" and to the "Valle de las Caides", and a "fiesta Campera". A sight-seeing programme for the participants and their guests who wish to see the surroundings of Madrid, the South of Spain, and Palma de Mallorca has also been organized.

For further information please write to:

Secretaria General, Dr. A. Juderias, Centro Nacional de Espedialidades Quirurgicas, Ciudad Universitaria, Madrid, Spain.

THE COLLEGE OF SPEECH THERAPISTS

The College of Speech Therapists is holding a Conference in Birmingham from July 24th to 28th, 1961.

Abnormalities of speech and language will be presented as systemic disorders under the guidance of the concepts of Signs, Signals and Symbols.

For further information please write to the Conference Organizing Secretary, 16 York Road, Birmingham 16.

BRITISH OTOLARYNGOLOGICAL CONGRESS

It is proposed to hold the first British Otolaryngological Congress in Great Britain in the summer of 1963 and an organizing committee is being set up for the purpose. It is expected that in addition to sessions for formal papers there will be a number of seminars on various topics and revision courses conducted by known authorities.

The Congress will probably last for five or six days.

Further details concerning time and place will be notified in this Journal in due course.

General Notes

SIXTH INTERNATIONAL CONGRESS OF AUDIOLOGY

THE sixth International Congress of Audiology will be held in Leyden, The Netherlands, from September 5th to 8th, 1962.

President: Prof. Dr. H. A. E. van Dishoeck;

Secretary Drs. A. Spoor.

In the program are planned three round-table talks, with associated and free papers.

The subject of the round tables are:

"Frequency analysis of the normal and pathological ear."
Moderator: Prof. Dr. G. von Békésy.
"Central deafness in children."
Moderator: Prof. Dr. J. M. Tato.
"Psychogenic deafness and simulation."
Moderator: Prof. Dr. H. A. E. van Dishoeck.

Official languages of the Congress are: English, French, German and Spanish.
Working languages will be: English and French.

The address of the secretariat is:

Ear-Nose-Throat Department,
Academisch Ziekenhuis,
LEIDEN (The Netherlands).

BACK JOURNALS REQUIRED AND FOR SALE

If any subscriber can spare copies of the January 1945 and June 1950 issues of the *Journal of Laryngology & Otology* they would be very much appreciated by the Librarian of The National Institute for the Deaf, 105 Gower Street, London, W.C.1.

If anyone would like to buy a set of the journals from 1921 to 1960 (mostly bound volumes), and the two relevant indexes, etc., please apply to Donald G. P. Macalister, 5 Clarendon Place, Leamington Spa.

THE MOUNT SINAI HOSPITAL

An intensive postgraduate course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty will be given January 13th, 1962 to January 26th, 1962 by Dr. Irving B. Goldman and staff at the Mount Sinai Hospital, New York in affiliation with Columbia University.

Candidates for the course should apply to Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29, N.Y.